REVIEW

Arch. Immunol. Ther. Exp., 2009, **57**, 95–104
PL ISSN 0004-069X
DOI 10.1007/s00005-009-0013-1

Autoimmunity and heart diseases: pathogenesis and diagnostic criteria

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Received: 2008.11.12, **Accepted:** 2008.12.05, **Published online:** 2009.03.31

Abstract

Autoimmunity may evolve in predisposed individuals following an exogenous trigger. Autoimmunity is affected by genetic, immune, hormonal, and environmental factors. Immune mechanisms in heart diseases are complex and often not completely understood. Several cardiac disorders are believed to be mediated by an immune reaction. Both humoral and cellular immunity are associated with the development of myocarditis, dilated cardiomyopathy, heart failure, rheumatic fever, and atherosclerosis. Here the diagnostic criteria and autoimmune aspects of autoimmune-mediated cardiac disorders are reviewed. New diagnostic criteria for "autoimmune dilated cardiomyopathy" were recently suggested by the authors. They presume that establishing a dominant autoimmune etiology in some patients will have clinical significance because these patients will potentially gain the greatest benefit from immunosuppressive and immunomodulating treatments.

Key words: autoantibodies, myocarditis, autoimmune dilated cardiomypathy, atherosclerosis, rheumatic fever.

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AUTOIMMUNITY

Autoimmunity may emerge in predisposed individuals following an exogenous trigger. Self antigens may be presented to the immune system following damage to myocardial tissue and cause an autoimmune response. Molecular similarity and subsequent cross-reactivity may cause autoimmunity following infections (Jahns et al. 2008). The induction of an autoimmune disease depends on genetic, immune, hormonal, and environmental conditions (Fig. 1) (Rahamim-Cohen et al. 2001; Shoenfeld et al. 2008b; Shoenfeld et al. 2008c). For example, estrogens, androgens, prolactin, vitamin D, and other hormones may affect autoimmunity (Shoenfeld et al. 2008b). Several immune-regulatory genes and tissue-specific genes are associated with autoimmunity predisposition (Shoenfeld et al. 2008b). Abnormalities in T-regulatory cells, Th1/Th2 switching, spontaneous polyclonal B-cell activation, and complement deficiencies may have important roles in autoimmunity (Rahamim-Cohen et al. 2001; Shoenfeld et al. 2008b). Autoantibodies may participate in the autoimmune process and are occasionally detected years before symptoms become apparent (Rahamim-Cohen et al. 2001; Shoenfeld et al. 2008a). In some cases, autoantibodies are associated with disease activity (Shoenfeld et al. 2008a). Autoimmune mechanisms may be found in several cardiovascular diseases, such as dilated cardiomyopathy (DCM), myocarditis, rheumatic fever, heart failure, and atherosclerosis. The immune factors are complex and not completely understood.

DILATED CARDIOMYOPATHY

DCM is a rare disease with an annual incidence of 0.005–10 new cases per 100,000 persons and a prevalence as high as 30–40 cases for the same population size (Caforio et al. 2008; Jahns et al. 2008; Rakar et al. 1997). It is defined as dilatation and impaired contraction of the myocardium. It may affect the left ventricle or the entire heart (Elliott 2000). DCM is a heterogeneous disease that may be caused by cardiotoxic substances, metabolic disorders, neuromuscular diseases, genetic factors, infections, nutritional states, and inflammatory conditions (Dec and Fuster 1994; Elliott 2000).

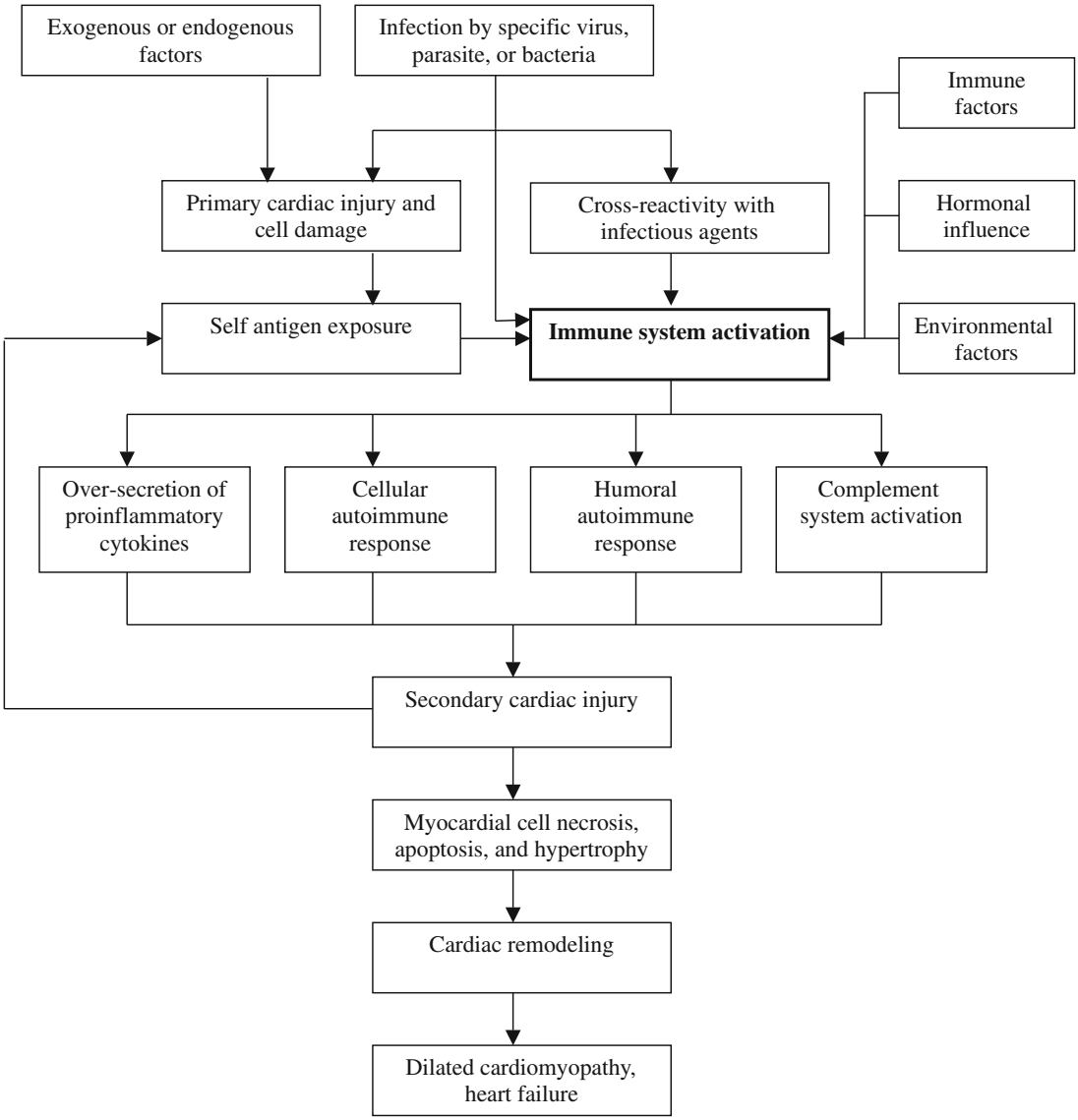

Fig. 1. Pathogenesis of heart failure due to immune-mediated response.

Nevertheless, a substantial portion (at least two thirds) of the cases remain "idiopathic" (Caforio et al. 2008; Jahns et al. 2008). DCM is a leading cause of cardiac transplantation in young adults (Caforio et al. 2008). The most common presenting symptom of DCM is symptomatic heart failure, usually with severe cardiac dysfunction (Dec and Fuster 1994). The mortality rate of patients with DCM is high, mostly due to heart failure and ventricular arrhythmias (Mestroni et al. 1999).

Autoimmune aspects

DCM may also appear in autoimmune rheumatic disorders such as systemic lupus erythematosus, dermatomyositis, systemic sclerosis, and Churg-Strauss syndrome (Dec and Fuster 1994; Elliott 2000; Usalan et al. 2007). Autoimmunity may be triggered by various exogenous factors (such as viral infections) in predisposed individuals (Jahns et al. 2008; Mobini et al. 2004). Relatives of DCM patients have a higher frequency of circulating anti-heart antibodies (Rose 2008), possibly predisposing them to developing DCM themselves (Caforio et al. 2007; Caforio et al. 2008; Jahns et al. 2008). There is some association between DCM and human leukocyte antigen (HLA)-DR4 (Caforio et al. 2008). Histologically, myocardial cell loss, fibrosis, and small clusters of lymphocytes may be present (Caforio et al. 2008; Dec and Fuster 1994; Rakar et al. 1997). The heart muscle stains positive for complement membrane--attack complex C5b-9, demonstrating that the complement system contributes to the immunological reaction (Eriksson and Penninger 2005).

In spite of major medical progress, the pathogenesis of DCM remains unknown. Several predisposing conditions may coexist, along with immune abnormalities. DCM patients might have autoantibodies against car-

diomyocytic membrane structures, receptors (i.e. anti-β1 adrenergic receptor (anti-β1AR) and anti-muscarinic receptor), cellular antigens (i.e. anti-myosin chain, actin, laminin, and anti-troponin), and mitochondrial antigens (i.e. antibodies against adenine nucleotide translocator, lipoamide, and pyruvate dehydrogenase) (Caforio et al. 2007; Elliott 2000; Fu 2008; Jahns et al. 2006; Jahns et al. 2008; Kallwellis-Opara et al. 2007; Mobini et al. 2004). Anti-β1AR autoantibodies are present in 30–40% of the idiopathic cases (Liang et al. 2008), compared with <1% in healthy individuals (Jahns et al. 2008). Some of these autoantibodies might have a role in the pathogenesis (Jahns et al. 2008). The findings of anti-cardiac autoantibodies provides *indirect* proof of autoimmunity (Fu 2008).

Autoantibodies may have a direct toxic effect on the myocardium. For instance, anti-β1AR antibodies may induce activation of caspase 3 and apoptosis of cardiomyocytes (Jahns et al. 2008; Levin and Hoebeke 2008; Liang et al. 2008). This effect can be blocked with pan-caspase inhibitor (Jahns et al. 2008). Some autoantibodies may have negative chronotropic effect (i.e. anti-cardiac M2 cholinergic receptor (anti-M2CR) via agonist action) (Jahns et al. 2008). Also, autoantibodies may trigger complement activation that causes myocardial damage. It may also increase the local concentration of tumor necrosis factor (TNF)-α, nitric oxide, active mitogen-activated protein kinases, and cytokines, which amplify myocardial damage (Elliott 2000; Kallwellis-Opara et al. 2007; Mobini et al. 2004). TNF-α causes a negative inotropic effect and apoptosis of cardiomyocytes (Mobini et al. 2004). Cell-mediated autoimmune response is another mechanism by which myocardial damage is caused when T cells are activated against cardiac self antigens (Jane-wit and Tuohy 2006; Mobini et al. 2004).

Additional evidence of autoimmunity in DCM can be found in mononuclear and T-lymphocyte infiltration and abnormal HLA class II expression on cardiac endothelium (Caforio et al. 2008). Moreover, the presence of known autoantigens, familial aggregation, and the existence of other familial autoimmune diseases support autoimmunity (Caforio et al. 2005; Elliott 2000; Eriksson and Penninger 2005; Limas et al. 2004). Proof of autoimmunity can be found in disease induction in SCID mice following transmission of anti-myosin CD4 T cells from mice with myocarditis (Caforio et al. 2005). Induction of an autoimmune response and DCM in animals subsequent to immunization with cardiac type α-myosin has also been established (providing *indirect* evidence for autoimmunity) (Caforio et al. 2005; Elliott 2000; Jahns et al. 2006). The infusion of anti-β1AR antibodies or immunization against β1AR in several animal models has been shown to cause DCM (Fu 2008; Levin and Hoebeke 2008). Obviously, disease induction following transfer of autoantibodies in human subjects has never been attempted. Therefore there is limited *direct* evidence of autoimmunity in idiopathic DCM in humans (although such proof is available in animal models). Furthermore, a review of the existing medical literature on the subject failed to show any report of transplacental transmission of immunoglobulins and secondary disease induction in newborns. Nonetheless, numerous other acknowledged autoimmune diseases have limited or no direct proof of their autoimmune basis (Rose and Bona 1993).

Diagnostic criteria

DCM may be diagnosed by echocardiography according to accepted criteria (Table 1) (Elliott 2000; Mestroni et al. 1999). Recently we proposed new diagnostic criteria for autoimmune DCM (Table 2) (Nussinovitch and Shoenfeld 2008b). Based on the new system of criteria system, the diagnosis of autoimmune-mediated DCM requires fulfillment of two major criteria and at least one minor criterion. We presume that the use of one minor criterion increases the sensitivity of the criteria system. The diagnosis of autoimmune DCM has a potential therapeutic significance because we believe that these patients will gain the greatest beneficial effects of immunosuppression, immunomodulating treatment, and immunoadsorption. The criteria system was proposed following the accumulation of data supporting the notion that autoimmunity has a key role in pathogenesis in some cases. We also presume that autoimmune DCM is a different clinical entity. The greatest downside of the proposed criteria is the limited practical use of some minor diagnostic criteria, mainly due to the fact that they require an invasive biopsy or special laboratory tests.

Therapy

Treatment should include conventional therapy for heart failure, such as renin-angiotensin-aldosterone system blocker, diuretics (not as mono-therapy), digoxin,

Table 1. Echocardiographic criteria for dilated cardiomyopathy (Elliott 2000; Mestroni et al. 1999)

Fulfillment of both criteria:
1. Ejection fraction <45% and/or fractional shortening <25%
2. Left ventricular end diastolic diameter (LVEDD) >112% than expected according to age and body surface area. Cut-off of LVEDD >117% is preferred in familial presentation
Exclusion criteria:
1. Blood pressure >160/100 mmHg
2. Intravascular obstruction of main coronary artery lumen exceeds 50%
3. Alcohol intake >80 g/day for males, >40 g/day for females
4. Persistent supraventricular tachyarrhythmia
5. Systemic disease
6. Pericardial disease
7. Congenital heart disease
8. Cor pulmonale

Table 2. Proposed diagnostic criteria for autoimmune-mediated dilated cardiomyopathy (DCM) (Nussinovitch and Shoenfeld 2008b)

Major:
1. Fulfillment of echocardiographic criteria for DCM
2. Excluding secondary cardiac injury because of infections, alcohol, toxins or chemotherapeutic drugs, metabolic abnormalities, nutritional deficiencies, neuromuscular diseases, or collagen vascular disorders
Minor:
1. Proven myocardial mononuclear cell infiltrate with abnormal HLA presentation
2. Circulating anti-heart autoantibodies or autoreactive lymphocytes in patients and in unaffected family members
3. *In situ* evidence of autoreactive lymphocytes and/or autoantibodies in cardiac tissue
4. Disease induction in an animal following transfusion of the patient's serum, antibodies, or lymphocytes
5. Proven clinical or echocardiographic improvement following immunoadsorption or immunosuppressive therapy
Supporting evidence, not considered criteria:
1. Clinical course of exacerbation and remissions
2. Positive HLA-DR4
3. Familial clustering of autoimmune diseases and/or family history of DCM (two or more affected individuals or sudden cardiac death in a first-degree relative younger than 35 years)

Diagnosis requires two major and at least one minor criteria.

beta-blockers, and warfarin in several indications (Dec and Fuster 1994; Mobini et al. 2004; Nussinovitch and Shoenfeld 2008b). Medical therapy has proved to significantly improve survival (Fu 2008). A defibrillator may be required in some patients (Nussinovitch and Shoenfeld 2008b). Nevertheless, the prognosis of patients with DCM remains poor despite intensive medical therapy. The presence of anti-β1AR autoantibodies is associated with higher rates of cardiovascular complications and sudden death due to ventricular arrhythmias (Fu 2008; Jahns et al. 2008). Heart transplantation remains the only definitive treatment for DCM patients (Elliott 2000; Nussinovitch and Shoenfeld 2008b). There is some possible evidence for a beneficial effect of immunoadsorption in cases of autoantibody-mediated DCM (Dorffel et al. 2000; Elliott 2000; Kallwellis-Opara et al. 2007; Muller et al. 2008). Immunoadsorption may improve myocardial contractility and ventricular dimensions (Levin and Hoebeke 2008), but further research is warranted before it can be considered a routine practice.

MYOCARDITIS

This is an acquired inflammatory condition involving the myocardial tissue that might cause myocardial dilatation and contractile dysfunction (Li et al. 2008). It may be subclinical or present with palpitations and chest discomfort, ECG changes, and syncope. Some patients develop myocardial failure which might progress to DCM. Sudden death may occur due to arrhythmias (Caforio et al. 2005; Caforio et al. 2008; Li et al. 2006). An exogenous trigger, such as Coxsackie virus B3 infection, might cause a chronic inflammation of autoimmune nature in predisposed individuals (Li et al. 2008). However, in some cases no such trigger is identified (Caforio et al. 2008). It was demonstrated that several mouse haplotypes predispose to severe myocarditis (H-2^a or H-2^s compared with the H-2^b haplotype), as well as other non-MHC genes (Rose 2008). Nonetheless, the genetic aspect of susceptibility to myocarditis in humans is still not entirely established (Li et al. 2008).

Autoimmune aspects

The immune mechanism that causes myocarditis and heart failure is not completely understood (Afanasyeva et al. 2004). Exposure of BALB/c mice to Coxsackie virus B3 or mouse cytomegalovirus may cause myocarditis in a double-phase process. It is presumed that the early phase is caused by a direct viral effect, while the second phase is autoimmune by nature (Krebs et al. 2007). Histologically, the late phase of myocarditis in the mouse model is characterized by a generalized mononuclear infiltration (Rose 2008). Myocarditis in mice can be mediated via T-cell action (i.e. BALB/c mice) or antibodies (i.e. DBA/2 mice) (Caforio et al. 2008). This finding supports the significance of poorly understood host factors in the pathogenesis. Autoantibodies against cardiac α and β myosin heavy chain, mitochondrial antigens, adenine nucleotide translocator, cardiac β1 adrenergic receptor and M2 muscarinic receptor, anti-branched chain α-ketoacid dehydrogenase dihydrolipoyl transacylase, and other autoantigens might participate in the pathogenesis (Afanasyeva et al. 2004; Li et al. 2008). Immunization against cardiac myosin heavy chain or infusion of anti-myosin autoantibodies in susceptible mice have caused myocarditis (Mascaro-Blanco et al. 2008; Rose 2008). Autoantibodies can cause apoptosis of cardiomyocytes or complement activation, direct cell-mediated cytotoxicity, or alter myocardial function (Afanasyeva et al. 2004; Mascaro-Blanco et al. 2008). In patients with chronic myocarditis, the levels of anti-myosin antibodies are associated with the extent of cardiac dysfunction (Li et al. 2006). It is unclear how antibodies against intracellular structures cause myocardial damage, although it is assumed that cross-reactivity to membrane antigens may occur (Li et al. 2006). There is evidence of cross-reactivity between anti-myosin autoantibodies and β1AR in the Lewis rat myocarditis model, which cause protein-kinase A signaling and cellular apoptosis (Caforio et al. 2008; Mascaro-Blanco et al. 2008). The complement system (C3d in particular) plays a key role in the pathogenesis of myocarditis (Rose 2008). Administration of cobra venom factor in mice prevents

myocarditis due to a decrease in C3 levels (Afanasyeva et al. 2004). An experimental mouse model disclosed a deposition of CD19 B cells, plasma cells, and IgG1 antibodies in the myocardial tissue (Afanasyeva et al. 2004). Following viral infections, cardiac plasma cells degranulate and release enzymes, such as tryptase chymase, stromelysin, and TNF-α. The granules can mediate rat cardiomyocyte apoptosis (Afanasyeva et al. 2004). Moreover, TNF-α and interleukin (IL)-1β may contribute to the pathogenesis, as it was proven that inhibition of either cytokine in susceptible mice prevents myocarditis (Rose 2008). On the other hand, decreased levels of interferon (IFN)-γ or IL-13 are associated with the development of severe late autoimmune disease in mice (Rose 2008). Both CD4 and CD8 Th cells are important mediators in the autoimmune process, while cytotoxic T lymphocytes can cause a direct Fas-ligand-mediated myocardial cell destruction (Afanasyeva et al. 2004). Injection of dendritic cells (activated via Toll-like receptors), which present myocardial peptides, induced CD4 T cell-mediated myocarditis in mice, supporting the possible cellular role in the pathogenesis (Eriksson et al. 2003).

Diagnostic criteria

The diagnosis of myocarditis requires tissue biopsy and the meeting of histological-immunohistochemical--immunological diagnostic criteria (Caforio et al. 2008). Viral myocarditis is diagnosed in the presence of a positive PCR test for viral genome (Caforio et al. 2008). The system of criteria for an autoimmune basis for myocarditis is based on the general criteria system for the diagnosis of autoimmunity proposed by Rose (Rose and Bona 1993).

An autoimmune basis of myocarditis is established by fulfilling two of the following diagnostic criteria (Table 3) (Caforio et al. 2005; Rose and Bona 1993): (1) abnormal HLA presentation in the myocardial tissue is accompanied by mononuclear infiltration, (2) anti-heart autoantibodies or autoreactive lymphocytes are isolated from the sera of patients and healthy family members, (3) autoreactive lymphocytes and/or autoantibodies are present in cardiac tissue, (4) autoantigen is involved in the pathogenesis, (5) transfusion of the patient's serum, antibodies, or lymphocytes causes disease induction in animals (Li et al. 2006), and (6) immunosuppressive therapy provides beneficial outcome.

Therapy

Some patients show spontaneous complete recovery. Others develop DCM and may need medical therapy for heart failure, or eventual cardiac transplantation (Caforio et al. 2005). It has been shown that the pathogenic effect of anti-cardiac myosin autoantibodies in mice can be blocked by cardiac myosin, anti-IgG, and inhibitors of β1 adrenergic receptor (Li et al. 2006). IL-10 has anti-inflammatory properties. Administration of recombinant human IL-10 to mice with experimental myocarditis resulted in improved survival and decreased myocardial TNF-α and IL-2 mRNA expression (Gong et al. 2007). The potential use of cytokine-altering therapy requires additional research, but poses a promising therapeutic approach. We suggest that immunomodulation should be investigated as a treatment modality for autoimmune-mediated myocarditis, either by immunoadsorption or by direct antibody blocking.

Table 3. Diagnostic criteria for immune-mediated myocarditis (Caforio et al. 2005; Rose and Bona 1993)

1. Abnormal HLA presentation in the myocardial tissue accompanied by mononuclear infiltration
2. Autoreactive lymphocytes and anti-heart autoantibodies are isolated from sera in patients and in healthy family members (such as anti-α and -β heavy chain, mitochondrial antigens, adenine nucleotide translocator, cardiac β1 adrenergic receptor and M2 muscarinic receptor, anti-branched chain α-ketoacid dehydrogenase dihydrolipoyl transacylase, and others)
3. Autoreactive lymphocytes and/or autoantibodies are present in cardiac tissue
4. Autoantigen is involved in the pathogenesis
5. Transfusion of the patient's serum, antibodies, or lymphocytes causes disease induction in an animal
6. Immunosuppressive therapy provides beneficial outcome

Diagnosis requires fulfillment of two criteria.

RHEUMATIC FEVER

During the last century there was a global decrease in rheumatic fever prevalence due to the wide use of antibiotics and improvement in living conditions (Carapetis et al. 2005). Nevertheless, rheumatic fever remains a major health problem in developing countries, with an annual incidence of hundreds of new cases per 100,000 children (2004; Carapetis et al. 2005). Ages 5–15 are the most commonly affected (2004). Autoimmune response to β-hemolytic streptococcal infection might cause long-term morbidity due to rheumatic heart disease (RHD) (Carapetis et al. 2005). The worldwide estimated annual death rate due to RHD in the year 2000 was as high as 332,000 (2004).

Autoimmune aspects

The immune response in rheumatic fever is reactive to infection by pharyngeal group A, class I streptococcal strains, which do not produce serum opacity factor (Carapetis et al. 2005). The group A streptococcus group can be subdivided according to more than 130 M-type proteins (2004). Despite major medical progress, the pathogenesis of rheumatic fever is not completely understood (Cilliers 2006). Only 0.3–3% of infected people will developed rheumatic fever, possibly indicating a prior genetic predisposition (2004). Association

between HLA type II and rheumatic fever was found in some populations (Guilherme et al. 2006). HLA-DR7, HLA-DR53, and some HLA-DQ were the most consistent with such association (Fae et al. 2005; Guilherme et al. 2007). There is controversy whether B-cell alloantigen (recognized by monoclonal antibody D8/17) increases susceptibility to the development of RHD. This notion might be true in some populations (2004; Carapetis et al. 2005). Gene polymorphisms have also been linked with increased risk of rheumatic fever, such as transforming growth-factor β-1, TNF-α, and Toll-like receptor-2 (Guilherme et al. 2007). Autoimmunity is triggered due to molecular mimicry between streptococcal α-helical M-protein (such as M5 protein) and group A carbohydrates to α/β cardiac myosin chains, tropomyosin, keratin, vimentin, and laminin (2004; Carapetis et al. 2005; Guilherme et al. 2006). Selected T-cell clones from the hearts of patients with RHD react both to cardiac proteins and to type 5 streptococcal M protein, supporting the principal of molecular mimicry and cross-reactivity in the disease's pathogenesis (Fae et al. 2005). In another study, a valvular disease with Aschoff-like bodies was induced in 50% of mice immunized with recombinant type 6 streptococcal M protein (Quinn et al. 2001). It is suspected that the autoimmune T-cell infiltration in RHD is accentuated by cytokine secretion due to streptococcal super-antigens such as exotoxin and, controversially, by M5-protein (Carapetis et al. 2005; Guilherme et al. 2006). It is believed that local T-cell secretion of IFN-γ in the endocardial tissue promoted fibrosis and valve deformity (Guilherme et al. 2006). Other cytokines, such as TNF-α and IL-10, are found both in endocardial and myocardial tissue, whereas IL-4 was reported in myocardial, but not endocardial tissue (Guilherme et al. 2007). Intra-myocardial levels of IL-1, IL-2, and TNF-α correlated with the progression of Aschoff-body formation (Guilherme and Kalil 2004). The streptococcus-induced autoimmune response to cardiac myosin heavy chain is also associated with myocarditis (Guilherme et al. 2006). It is believed that the valvular damage is caused by a cross-reaction of T cells to laminin, an essential basement membrane component, and an autoimmune response against vimentin in the inner valve (Carapetis et al. 2005; Guilherme et al. 2006). Another cause of valvular lesion is the autoimmue action of several anti-heart antibodies (AHAs), with cross-reactivity to streptococcal M-protein and group A carbohydrates (anti-streptococcal N-acetyl-β-D glucosamine antibodies) (Carapetis et al. 2005; Guilherme et al. 2006). AHAs can persistently circulate in the serum for years following rheumatic fever (Guilherme et al. 2006). High and persistent levels of anti-group-A carbohydrate antibodies are associated with poor cardiac outcome of chronic valvulitis (Guilherme et al. 2006).

Diagnostic criteria

The diagnostic criteria of rheumatic fever, also known as the Jones Criteria, are well known and commonly used (1992). They have been modified four times since they were originally published (Saxena 2000). The diagnosis is established by the presence of two major or one major and two minor criteria, in addition to laboratory evidence for a recent β-hemolytic streptococcal infection. The major criteria are (a) carditis, (b) polyarthritis, (c) Sydenham's chorea, (d) erythema marginatum, and (e) subcutaneous nodules. The minor criteria are (a) arthralgia, (b) fever, (c) elevated erythrocyte sedimentation rate or C-reactive protein (CRP), and (d) prolonged P-R interval (Table 4) (2004; Carapetis et al. 2005; Cilliers 2006; Sherer and Shoenfeld 2008). It has been suggested that carditis should be sought by using routine echocardiography, as its sensitivity is up to 10 times higher than auscultation alone (2004; Sherer and Shoenfeld 2008). Nevertheless, the use of echocardiography in an acute setting and as a possible diagnostic criterion remains controversial (2004).

Therapy

Penicillin treatment for group-A streptococcal pharyngitis is considered the main preventive means for rheumatic fever. Penicillin is also used as post-rheumatic fever secondary prophylaxis, although it has not been proven to alter cardiac outcome (Carapetis et al. 2005). A four-week bed rest is recommended in cases of carditis (2004). Salicylates, which are used for acute rheumatic fever, do not prevent residual RHD (2004; Carapetis et al. 2005). Further research is warranted in order to evaluate the long-term therapeutic effect of corticosteroids and other new anti-inflammatory drugs in the treatment of acute rheumatic fever (2004; Carapetis et al. 2005). Corticosteroids are not superior to aspirin, and vice versa, in the prevention of cardiac complication (Cilliers 2006). Intravenous immunoglobulins (IVIg) do not reduce valvulitis or alter the natural history and are therefore not recommended in this setting (Nussinovitch and Shoenfeld 2008a). Several anti-group A streptococcus vaccines are being developed, although it is expected that M-serotype diversity

Table 4. Jones' revised criteria for the diagnosis of rheumatic fever

Major:
1. Carditis
2. Polyarthritis
3. Sydenham's chorea
4. Erythema marginatum
5. Subcutaneous nodules
Minor:
1. Arthralgia
2. Fever
3. Elevated erythrocyte sedimentation rate or CRP
4. Prolonged P-R interval

Diagnosis requires 2 major or 1 major and 2 minor criteria in addition to laboratory proof for a recent β-hemolytic streptococcal infection.

will limit their efficacy (Carapetis et al. 2005). Heart failure due to rheumatic fever carditis should be treated with diuretics, angiotensin converting enzyme (ACE) inhibitors, and digoxin along with other conventional treatments (2004).

HEART FAILURE

Heart failure may be the result of a heterogonous group of disorders which includes ischemic diseases, valvular failure, myocardial infections, chemical and toxic injuries, immune disorders, and others. The overall prevalence of heart failure has increased in the last decades, in part due to major improvements in cardiovascular disease management (Celis et al. 2008). Currently over 20% of hospital admissions in the United States are related to heart failure manifestations (Jessup and Brozena 2003).

Autoimmune aspects

Accumulating evidence supports the notion that immune activation and systemic proinflammatory state are important in heart failure pathogenesis (Gong et al. 2007). Myocardial infarction (as an example of a common cause of heart failure development) is followed by inflammatory cellular infiltration in the infracted area and elevation of autoantibodies against cardiac proteins in the circulation(Torre-Amione 2005). Complement activation amplifies the damage to myocardial tissue (Frantz et al. 2005). A correlation was found between elevated CRP levels and mortality in heart failure patients (Gong et al. 2007).

Regardless of the nature of the initial cardiac injury, it may result in the presentation of self antigens to the immune system and both cellular and humoral responses (Celis et al. 2008). Severe heart failure is a proinflammatory state in which there is an increase in both circulating and myocardial cytokines such as IL-1, IL-6, IL-18, and TNF-α (Nussinovitch and Shoenfeld 2008a; Piepoli 2007). IL-10 levels were shown to be lower in DCM than in patients with ischemic cardiomyopathy (Lindberg et al. 2008). Inflammatory mediators cause direct myocardial suppression and facilitate cardiac remodeling due to cardiomyocytic hypertrophy, necrosis, and apoptosis (Gong et al. 2007; Piepoli 2007). Moreover, activation of the complement system, production of autoantibodies, and over-expression of MHC class II in the involved tissue may occur and promote inflammation (Torre-Amione 2005).

Diagnostic criteria

Heart failure is usually classified as a metabolic demand that is higher than cardiac output. In 20–50% of heart failure cases, normal cardiac output and systolic function exist along with diastolic failure, as occurs in cases of hypertension, diabetes, and morbid obesity with obstructive sleep apnea (Desai and Fang 2008; Jessup and Brozena 2003). Moreover, the so-called failing heart could be in the presence of normal myocardial function and secondary to high metabolic demand in cases such as thyrotoxicosis, beriberi, and pregnancy. The diagnosis of heart failure requires clinical assessment and quantitative echocardiographic measurements of cardiac anatomy and function.

Therapy

Symptomatic heart failure usually carries a poor prognosis (Jessup and Brozena 2003). Treatment includes risk factor reduction, ACE inhibitors, beta-blockers, diuretics, digoxin, cardiac resynchronization therapy for selected patients, and aldosterone antagonists and other, invasive therapies such as heart transplantation and a ventricular assist device (Jessup and Brozena 2003). Attempts to modulate inflammation by specific anti-TNF-α agents (etanercept, infliximab) were discontinued due to lack of clinical benefit in humans (Aukrust et al. 2006; (Nussinovitch and Shoenfeld 2008a). Pexelizumab, a humanized monoclonal antibody against C5 (that prevents C5b-9 complex formation), was used in acute myocardial infarction settings with no beneficial clinical outcome despite promising results in a rat model (Frantz et al. 2005). Methotrexate (MTX) as monotherapy for rheumatoid arthritis patients has decreased the risk of heart failure and cardiovascular mortality in anecdotal reports (Gong et al.2007). Moreover, a low-dose MTX therapy for heart failure patients resulted in an anti-inflammatory state and improved New York Heart Association (NYHA) functional class. However, no change in ejection fraction was noted (Gong et al.2007). IVIg treatment for NYHA II/III patients caused a decrease in the systemic inflammatory state and a significant increase in left ventricular ejection fraction which did not sustain one year after discontinuation of treatment (Nussinovitch and Shoenfeld 2008a). It is speculated that the beneficial effect of IVIg in the subgroup of heart failure patients was due to an immunomodulating effect on the proinflammatory cytokines and anti-idiotype properties for neutralizing pathogenic autoantibodies (Nussinovitch and Shoenfeld 2008a).

Immunoadsorption in one study resulted in a dramatic improvement in ejection fraction from 22 to 38%. It is not completely understood whether the elimination of anti-β1AR antibodies or other antibodies is responsible for the outcome (Celis et al. 2008; Torre-Amione 2005). Immunoadsorption have been shown to decrease the number of myocardial lymphocytes and HLA class II expression (Felix and Staudt 2008). Immune modulating therapy (IMT) by autologous *ex vivo* exposure of blood to oxidative stress, UV radiation, and elevated temperature causes anti-inflammatory cytokine release from the apoptotic cells (Celis et al. 2008; Gong et al. 2007). The blood is later transfused intramuscularly (Celis et al. 2008; Gong et al. 2007; Torre-Amione

2005). IMT was found to improve NYHA class as well as cause death risk reduction in heart failure patient subgroups without altering ejection fraction (Celis et al. 2008; Gong et al. 2007). Several novel treatments with anti-inflammatory properties, including growth hormone and androgens, require further research.

ATHEROSCLEROSIS

Atherosclerosis is a process that usually starts in childhood with a possibly grave clinical outcome later in life due to cardiovascular diseases. Atherosclerosis is a multifactorial disease that is increasingly considered in part as an immune-mediated process (Shoenfeld et al. 2005; Shoenfeld et al. 2001). This notion is supported by the presence of activated lymphocytes, macrophages, and immunoglobulins in the forming atherosclerotic plaque (Afek et al. 2000; Sherer and Shoenfeld 2002). CRP is commonly high in autoimmune disease (de Leeuw et al. 2005). There is a proven correlation between CRP levels and the risk of atherosclerosis and cardiovascular disease (Shoenfeld et al. 2001; Singh et al.2008). Moreover, about 40% of individuals with cardiovascular morbidity have no conventional risk factor, indicating an alternative mechanism in the pathophysiology of atherosclerosis (Shoenfeld et al. 2001). Atherosclerosis is accelerated in several autoimmune and rheumatic diseases, such as rheumatoid arthritis (Szekanecz et al. 2007), systemic lupus erythematosus, systemic sclerosis (Sherer et al. 2007), Wegener's granulomatosis (de Leeuw et al. 2005), and antiphospholipid syndrome (APS) (Belizna et al. 2007).

Autoimmune aspects

Several autoimmune features exist in the atherosclerotic process: autoantigens have been detected, such as heat-shock proteins (HSPs), β2-glycoprotein-I (β2GPI), and oxidized low-density lipoproteins (oxLDL) (Sherer and Shoenfeld 2002; Shoenfeld et al. 2005). Auto-antibodies against those autoantigens participate in the pathogenesis (Sherer and Shoenfeld 2002; Shoenfeld et al. 2001). There is a correlation between anti-oxLDL antibody titer and the extent of atherosclerosis, cardiovascular complications, and the risk of re-stenosis following angioplasty (Shoenfeld et al. 2005; Shoenfeld et al. 2001).

Antibody against β2GPI increases oxLDL uptake by macrophages in the plaque, thereby increasing foam-cell formation (Shoenfeld et al. 2001). The presence of autoantibodies against β2GPI\oxLDL in APS is associated with increased risk of arterial thrombosis (Matsuura et al. 2002). Atherosclerosis is accelerated by immunization with autoantigens, as observed in animals injected with HSP-65 or β2GPI (Afek et al. 2000; George et al. 2000; Sherer and Shoenfeld 2002). Moreover, transfer of lymphocytes from mice immunized against β2GPI to LDL-R-deficient mice caused accelerated atherosclerosis (George et al. 2000; Shoenfeld et al. 2001).

SCID mice or $CD4^+$ and $CD8^+$ T cell-depleted mice have decreased atherosclerosis, supporting the significance of immunity in the atherosclerotic process (Shoenfeld et al. 2005). On the other hand, the immunosuppression achieved by treating C57BL/7 mice with cyclosporin A was accompanied by accelerated atherosclerosis (Sherer and Shoenfeld 2002). This observation implies that the cellular immune system might have a protective role against atherosclerosis in some cases. Several cytokines are secreted in the plaque, including IL-1, IL-6, IL-8, TNF-α, and IFN-γ (Nussinovitch and Shoenfeld 2008a; Shoenfeld et al. 2005). IL-10 deficiency in mice increases the risk of atherosclerosis (Nussinovitch and Shoenfeld 2008a).

Therapy

In addition to traditional anti-atherogenic drugs such as statins, immunosuppression or immunomodulating therapy could be a possible future treatment modality. This notion is supported by the observation that mycophenolate mofetil, an immunomodulator, decreased atherosclerotic plaque formation in a rabbit model (Belizna et al. 2007). Nevertheless, the net effect of immunosuppression may be pro-atherosclerotic, as observed following cyclosporine A administration (Sherer and Shoenfeld 2002). Immunomodulation can be achieved by IVIg administration. IVIg causes an increase in IL-10 (Nussinovitch and Shoenfeld 2008a). IVIg also contains anti-oxLDL, anti-anti-oxLDL, and anti-CD40 ligands and other natural immunoglobulins with a possible anti-idiotype effect (Nussinovitch and Shoenfeld 2008a; Shoenfeld et al. 2001). Overall, IVIg administration favors an anti-atherogenic outcome (Nussinovitch and Shoenfeld 2008a; Sherer and Shoenfeld 2002). Immunomodulation is also achieved by statins, which decrease the expression of MHC class II and adhesion molecules on the vascular walls (Shoenfeld et al. 2001).

Acknowledgment: We wish to thank Tamar Ben-Artzi for her editorial assistance.

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