The General Practice Guide to Autoimmune Diseases

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Autoimmunity in myocarditis and dilated cardiomyopathy

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1 Introduction

Myocarditis and dilated cardiomyopathy (DCM) are considered by some investigators as the acute and chronic stages of the same disease. The reported prevalence of idiopathic DCM in the USA is 36 cases per 100 000 persons. The annual incidence of idiopathic DCM was reported to be 5–8 new cases per 100 000 persons. In most idiopathic DCM cases, clinical presentation first appears between the ages of 20–50. DCM is the leading cause of cardiac transplantation requirement in young adults. Indeed, some patients with myocarditis will ultimately develop DCM, although others may completely recover without chronic complications.

Myocarditis is an acquired inflammatory condition involving the myocardial tissue. Although myocarditis is largely associated with viral infections, some cases remain idiopathic, while in others there is convincing evidence of autoimmune pathophysiology. It is unknown as to why specific individuals are more susceptible to developing autoimmune heart diseases. The male to female ratio has been reported as 1.2–2 : 1 and 2.5 : 1 in autoimmune myocarditis and idiopathic DCM, respectively. Autoimmunity is influenced by genetic, immune, hormonal and environmental factors. Myocardial injury (due to infection, ischaemia, inflammation, toxins or other cardiotoxic factors) may trigger exposure to autoantigens, subsequently, initiating an autoimmune response, causing myocarditis and DCM. Nevertheless, in some myocarditis/DCM cases no specific trigger is found.

2 Diagnostic measurements for experts

Clinically, myocarditis may be asymptomatic or present with chest pain, palpitations, ECG changes, syncope, arrhythmias, and in some cases, sudden death. Early diagnosis may be extremely challenging since signs and symptoms may be unspecific (Table 1). Clinically, DCM is most commonly characterized as symptomatic heart failure. Prior to confirmation of a diagnosis of autoimmune my-

ocarditis/DCM, proof of autoimmunity may be required. Evidence of autoimmune myocarditis/DCM may be found in a mononuclear cell infiltrate presenting with an abnormal human leukocyte antigen (HLA), presence of circulating anti-heart autoantibodies (AHA) or autoreactive lymphocytes in patients, and in unaffected family members, and in in-situ evidence of autoreactive lymphocytes and/or autoantibodies in cardiac tissue.

Table 1. Signs and symptoms of myocarditis and dilated cardiomyopathy.

– History of an upper respiratory illness or recent viral infection in some patients (in myocarditis)
– A number of myocarditis cases are subclinical
– Asymptomatic cardiomegaly
– Symptomatic left- and right- heart failure
– Physical examination findings consistent with heart failure
– Chest pain on exertion, or at rest
– Dyspnoea on exertion, or at rest
– Fatigue
– Palpitations and arrhythmias (both ventricular and supra-ventricular)
– Peripheral pitting oedema
– Systemic and pulmonary embolisms
– Syncope
– Elevated serum levels of myocardial enzymes (in myocarditis)
– Electrocardiographic changes
– Sudden death

3 Requirements for family practitioners

Diagnosis should be made in the early stages of the disease in order to identify, control, and treat possible complications. Distinguishing autoimmune myocarditis/DCM from non-autoimmune diseases has limited practical implications currently. Nevertheless, we believe that in the future, specific immuno-modulating therapies will be available for proven autoimmune cases. Diagnosis of autoimmune DCM may require clinical, echocardiographic and laboratory findings (Table 2). Also, exclusion of other causes of myocardial inflammation and cardiomyopathy is important before autoimmune pathophysiology can be concluded. In light of

familial clustering in some cases, the physician should evaluate whether other family members were or are currently affected. Clinical courses of exacerbation and remission may provide supportive evidence of autoimmunity. Despite extensive evaluations, approximately 50 %–80 % of DCM cases remain idiopathic.

Table 2. Diagnostic criteria for autoimmune dilated cardiomyopathy.

Clinical criteria for diagnosing dilated cardiomyopathy (all criteria must be fulfilled).

1. Ejection fraction < 45 % and/or fractional shortening < 25 %
2. Left ventricular end diastolic dimension (LVEDD) > 112 % than expected according to age and body surface area. Cutoff of LVEDD > 117 % is preferred in familial presentation
3. Exclusion of the following: blood pressure > 160/100 mmHg, intravascular obstruction of main coronary artery lumen exceeds 50 %, alcohol intake > 80 g/day for males, or > 40 g/day for females, persistent supraventricular tachy-arrhythmias, systemic disease, pericardial disease, congenital heart disease and cor pulmonale

Proposed laboratory criteria for autoimmune dilated cardiomyopathy (diagnosis requires fulfilment of at least one criterion)

1. Proven mononuclear cell infiltrate with abnormal human leukocyte antigen (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 tissues
4. Disease induction in animals following transfusion of the patient's serum, antibodies, or lymphocytes
5. Proven clinical or echocardiographic improvement following immunoadsorption or immunosuppressive therapy

Supporting evidence for autoimmune dilated cardiomyopathy, not considered criteria

1. Clinical course of exacerbations and remissions
2. Positive HLA DR4
3. Familial clustering of autoimmune diseases and/or family history of dilated cardiomyopathy (two or more affected individuals, or sudden cardiac death in a first-degree relative < 35 years old)

Clinically, signs of heart failure might be found upon physical evaluation, including liver congestion, hepatomegaly, lower limb oedema, jugular venous distension, pulmonary oedema, etc. Third and fourth heart sounds are common in DCM. Pericardial friction rub may be found in patients with peri-myocarditis. Chest X-rays may reveal cardiomegaly and pulmonary congestion.

ECG changes may be non-specific and include ST-T changes, Q-waves, atrioventricular conduction delay, bundle branch block, supraventricular arrhythmias and occasionally low voltage (Fig. 1).

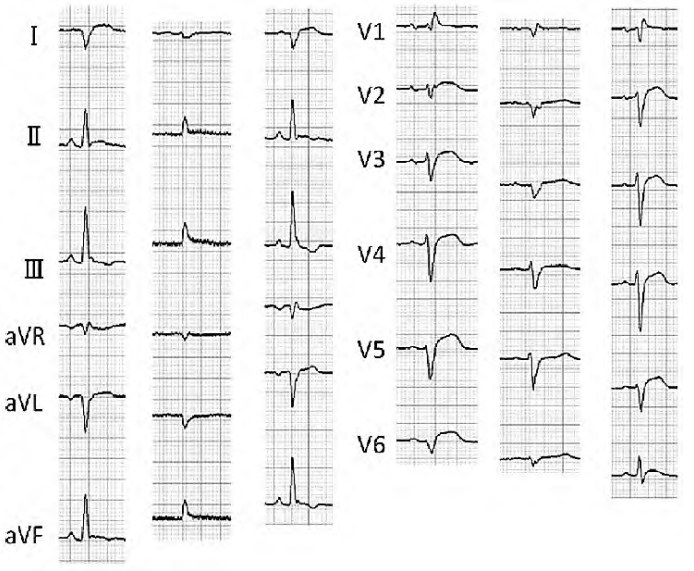

Figure 1. Electrocardiogram at admission, acute phase, and recovery phase of myocarditis (Case Study). At admission, convex ST-segment elevations in the precordial leads were seen. Although the voltage of all leads were reduced at the acute phase, the ECG completely returned to the prior findings. (*Adopted with permission from Yuya Matsue, Leon Kumasaka, Wataru Nagahori, et al. 2010. A case of fulminant myocarditis with three recurrences and recoveries. Int Heart J 51: 218–219.*)

Echocardiography might demonstrate cardiac dilatation and poor systolic function. Fulfilment of echocardiographic criteria (Table 2) is crucial in diagnosing DCM.

Clinical investigation in cases of myocarditis should endeavour to identify a trigger, such as isolation of a cardiomyopathic viral agent or identification of sero-conversion against a known cardiac pathogen.

Diagnosis of myocarditis may require referral to a medical facility to perform a cardiac biopsy, which would prove cellular infiltration and cardiomyocyte necrosis.

Absence of angiographically significant coronary artery disease may also assist in excluding ischaemic pathophysiology.

Fulminant myocarditis and other decompensating conditions should be treated in specialized hospital units.

4 Follow up

Clinical observations

The clinician should observe the patient's clinical performance and screen for contractile deterioration and increased risk of arrhythmias via extended ECG monitoring, and electrocardiographic arrhythmogenic markers. The presence of specific circulating AHA (such as anti-β1 adrenergic receptor autoantibodies) may also be associated with arrhythmias and poor prognosis.

Expectations

The majority of myocarditis patients will clinically improve and survive. Approximately 25 % of DCM patients will stabilize or spontaneously improve. Nevertheless, once DCM has developed, particularly in older patients, prognosis may be unfavourable. Heart transplantation may be offered as a definitive treatment.

Blood tests

Anticoagulation effectiveness should be monitored by periodic INR measurement to prevent embolisms. Serologic investigations for infectious agents (most of which are viral) may assist in diagnosing an infectious trigger. Moreover, serological investigations of AHA may provide further evidence of autoimmunity. It remains to be explored whether changes in the AHA titre throughout follow-up has any prognostic implications.

5 Management

In the acute phase of myocarditis, physical exercise should be avoided. In cases where contractile dysfunction has evolved, appropriate therapy for heart failure should be initiated (i. e., salt-restriction, renin-angiotensin-aldosterone system blockers, diuretics, β-blockers, and digitalis). Patients should avoid exposure to cardiotoxic agents and alcohol. Warfarin should be taken in cases of atrial fibrillation, severe ventricular dysfunction, and past history of thromboembolism. Anti-arrhythmic drug therapy has resulted in conflicting outcomes, and in some cases has triggered or aggravated arrhythmias. Therefore, clinicians usually discourage their use in preventing arrhythmias. Severe heart failure may ultimately require left ventricular assisted devices and heart transplantation. Some patients

will require defibrillator implantation in an attempt to control recurrent ventricular arrhythmias. Cardiac resynchronization therapy may be beneficial in heart failure and intra-ventricular conduction delay.

Specific and non-specific immune-modulating therapies represent possible future treatment strategy regarding autoimmune myocarditis and DCM. Such therapeutic approaches include immunosuppression, immunoadsorption, intravenous immunoglobulins, cytokines-altering therapy, immunisation against autoantigens, or treatment with other specific peptides that modulate a specific immune response. Nevertheless, most of these therapeutic approaches remain experimental and theoretical. The effectiveness of non-specific immunosuppression is unclear.

6 Diagnostic tests

Cardiac magnetic resonance (CMR) imaging in myocarditis may demonstrate diffuse patchy mid-myocardial and epicardial late gadolinium enhancement, and sparing of the subendocardium.

Immunological evaluation may require a myocardial biopsy to evaluate whether cardiac deposition of auto-reactive lymphocytes and/or autoantibodies exists. In addition, circulating AHA should be evaluated. Autoimmunity may also be established by induction of cardiac disease in a laboratory animal following transfusion of the patient's sera, antibodies or lymphocytes.

7 Testing methods (benefits, limitations)

Definitive diagnosis of autoimmune cardiac myocarditis/DCM is mainly limited by the necessity for invasive procedures such as an endo-myocardial biopsy. There are several techniques available for detecting AHA (i. e., Elisa, immunoassay, surface plasmon resonance measurements, and functional assays), although a gold standard is lacking. In addition, there are no strict criteria as to the definition of abnormal autoantibodies titre. Therefore, future research should focus on laboratory tests' standardisation in the detection of autoimmune markers. The possible benefits from such standardisation may be earlier diagnosis of autoimmune illnesses and earlier treatment with targeted therapy.

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Abbreviations

DCM, dilated cardiomyopathy; **AHA**, anti-heart antibodies; **CMR**, cardiac magnetic resonance.