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REVIEW

Myocarditis: A Rheumatologic Perspective

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ABBREVIATIONS:
ACE = angiotensin converting enzyme
ANA = antinuclear antibodies
ANCA = anti-neutrophil cytoplasmic antibodies
AV = atrioventricular
BNP = brain natriuretic peptide
CCP = cyclic citrullinated peptide
CMR = cardiac magnetic resonance
CSS = Churg Strauss syndrome
CTDs = connective tissue diseases
cTn = cardiac troponin(s)
DM = dermatomyositis
DNA = deoxyribonucleic acid
dsDNA = double stranded DNA
ECG = electrocardiogram
EGPA = eosinophilic granulomatosis with polyangiitis
GPA = granulomatosis with polyangiitis
IM = inflammatory myopathies
LGE = late gadolinium enhancement
LV = left ventric-le(-ular)
PM = polymyositis
SLE = systemic lupus erythematosus
RA = rheumatoid arthritis
SSc = systemic sclerosis
TGF = transforming or tumor growth factor
TNF = tumor necrosis factor

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ABSTRACT

Myocarditis is an uncommon complication in patients with autoimmune rheumatic diseases. Due to paucity of clinical data, information has mostly been derived from postmortem findings. The mechanism of myocardial damage in connective tissue diseases depends on the pathophysiology of the underlying disease. Systemic inflammation, impaired microvascular circulation and vasculitis affect myocardial remodeling process, cause repeated focal ischemia resulting in hypertrophy, fibrosis of the myocardium and the conductive system, all resulting in reduced contractility. Additionally, immunological abnormalities, coexisting myositis and the degree of disease activity are predictors of myocarditis progression. Clinical presentation ranges from subclinical to severe, life-threatening form. Early recognition is important for institution of appropriate immunomodulatory therapy.

INTRODUCTION

Myocarditis is an inflammatory reaction of the myocardium to various infectious, toxic or autoimmune causes, mainly characterized by inflammatory infiltration and cardiomyocyte necrosis.[1] The data in the literature about myocarditis in connective tissue disorders (CTDs) are limited and most of our knowledge derives from postmortem findings.[2] However, it is considered a rare, under-recognized, under-treated and potentially fatal complication.[5] The mechanism of myocardial damage among CTDs differs according to the pathophysiology of the underlying disease. Myocarditis due to autoimmune disorders should be urgently recognized because of the likely progression of the cardiac injury to heart failure or ventricular remodeling with serious and/or life threatening complications.[3] The autoimmune rheumatic diseases that can be complicated by myocarditis comprise systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), anti-neutrophil cytoplasmic antibodies (ANCA)-related vasculitides, inflammatory myopathies (IM), systemic scleroderma (SSc) and sarcoidosis. The main mechanisms that are involved in myocardial damage in CTDs are systemic inflammation, microangiopathy and vasculitis (Table 1).[4,5] Immunological abnormalities, coexisting myositis and degree of disease activity are additional predictors for the prognosis of myocarditis. The above mechanisms affect the myocardial remodeling process by causing repeated focal ischemia, resulting in hypertrophy and fibrosis in both myo-

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TABLE 1. Mechanisms of Myocardial Damage Among Connective Tissue Diseases (CTDs)

Disease	Inflammation	Vasculitis	Microangiopathy
SLE	✓	✓	
RA	✓		
SSc			✓
IM	✓		
EGPA	✓	✓	
GPA	✓	✓	
Sarcoidosis	✓		

EGPA = eosinophilic granulomatosis with polyangiitis; GPA = granulomatosis with polyangiitis; IM = inflammatory myopathies; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus; SSc = systemic sclerosis.

cardium, conductive system and thus reduced contractility.[5,6]

The clinical presentation varies in severity and type of symptoms. The spectrum ranges from asymptomatic (subclinical) form to significant, sometimes life-threatening disturbance of cardiac function.[9] The great heterogenicity in clinical expression is interpreted according to the location and extent of damage.[5] However, manifestations range from mild dyspnea or chest pain that subside without specific therapy, to sudden death, with new onset arrhythmias and complete heart block, hemodynamic instability and cardiovascular collapse or an acute myocardial infarction-like syndrome. Fatigue and diminished exercise tolerance, because of low cardiac output, and palpitations may also occur.[7] Physical findings include a resting tachycardia, jugular vein distention, murmurs and diminished intensity of the first heart sound.[8]

The diagnosis of autoimmune myocarditis depends on clinical suspicion, because of the lack of definite diagnostic tests and a standardized process (Fig. 1). Serum biomarkers of myocardial injury, such as creatine kinase or cardiac troponins, are routinely measured when myocarditis is suspected, but are only helpful early in its course. Creatine kinase or its cardiac specific (MB) isoform has low predictive value, while troponins have limited sensitivity (34-50%), but high specificity (close to 90%) for the diagnosis of myocarditis.[10]

The electrocardiogram may show sinus tachycardia, ST segment and T-wave abnormalities, atrial and ventricular arrhythmias, atrioventricular (AV) block and conduction defects.[11] The echocardiographic findings, mainly suggesting the presence of myocarditis, are left ventricular (LV) segmental or global dysfunction and LV dilatation. Right ventricular dysfunction is a predictor of adverse outcome.[12] Nuclear imaging techniques (gallium and indium-111) lack specificity for myocarditis detection.[13] Endomyocardial biopsy, an invasive technique, is considered the gold standard for the diagnosis but it is not routinely performed because of the procedure related risks and its limited sensitivity due to sampling error.[7] Cardiovascular magnetic resonance (CMR) imaging enables diagnosis of myocarditis by detecting edema, myocyte necrosis, fibrosis, changes in ventricular size and wall motion abnormalities.[5] CMR detects subclinical forms of disease and allows early initiation of targeted therapy.[5,7] Early recognition of myocarditis in autoimmune diseases is of great importance because its severity specifies the immunomodulatory treatment.[9,14]

SYSTEMIC LUPUS ERYTHEMATOSUS

Systemic lupus erythematosus (SLE) is a complex autoimmune, inflammatory multisystem disease characterized by immune complex deposition, production of autoantibodies and considerable heterogeneity in clinical manifestations, laboratory findings and disease outcome. Patients may present with any organ system involvement, such as arthritis, serositis, skin rash, glomerulonephritis and neurological symptoms.[15,17] Frequent laboratory abnormalities include anemia, leucopenia, lymphocytopenia and thrombocytopenia.[15,16] Patients may have positive antibodies which are directed against various nuclear antigens such as nucleosomes, histones, antinuclear antibodies (ANA), double-strained DNA antibodies (anti-dsDNA) and ribonucleoproteins.[15,16] The disease incidence is higher in young women. A variety of genetic, environmental and hormonal factors have been identified as possible risk factors for developing SLE. Early diagnosis, intense therapy and alternative strategies in treating comorbidities contribute to improvement of disease prognosis.

Lupus myocarditis is infrequent; its overt clinical detection ranges from 3-15%, although its frequency in autopsy studies is higher, supporting the subclinical presentation of disease.[14,18] In SLE, immune-complex mediated small vessel vasculitis and/or inflammatory infiltration result in secondary cardiomyocyte injury.[14] Circulating antibodies may also contribute to this process by directly affecting the myocardial tissue. Anticardiolipines, anti-Ro and anti-ribonucleoprotein antibodies, are associated with left ventricular dysfunction.[19,20] Peripheral skeletal myositis increases risk for developing myocarditis. Acute myocarditis may accompany other manifestations of SLE, particularly pericarditis.

Myocardial biopsy was thought to be the gold standard method for diagnosis of lupus myocarditis. However, this is an invasive procedure associated with certain risks. Histologic findings show small foci of fibrinoid necrosis, interstitial mononuclear cell infiltrates, while immunofluoroscence studies demonstrate immune complex and complement deposition in the walls and perivascular tissues of myocardial vessels,

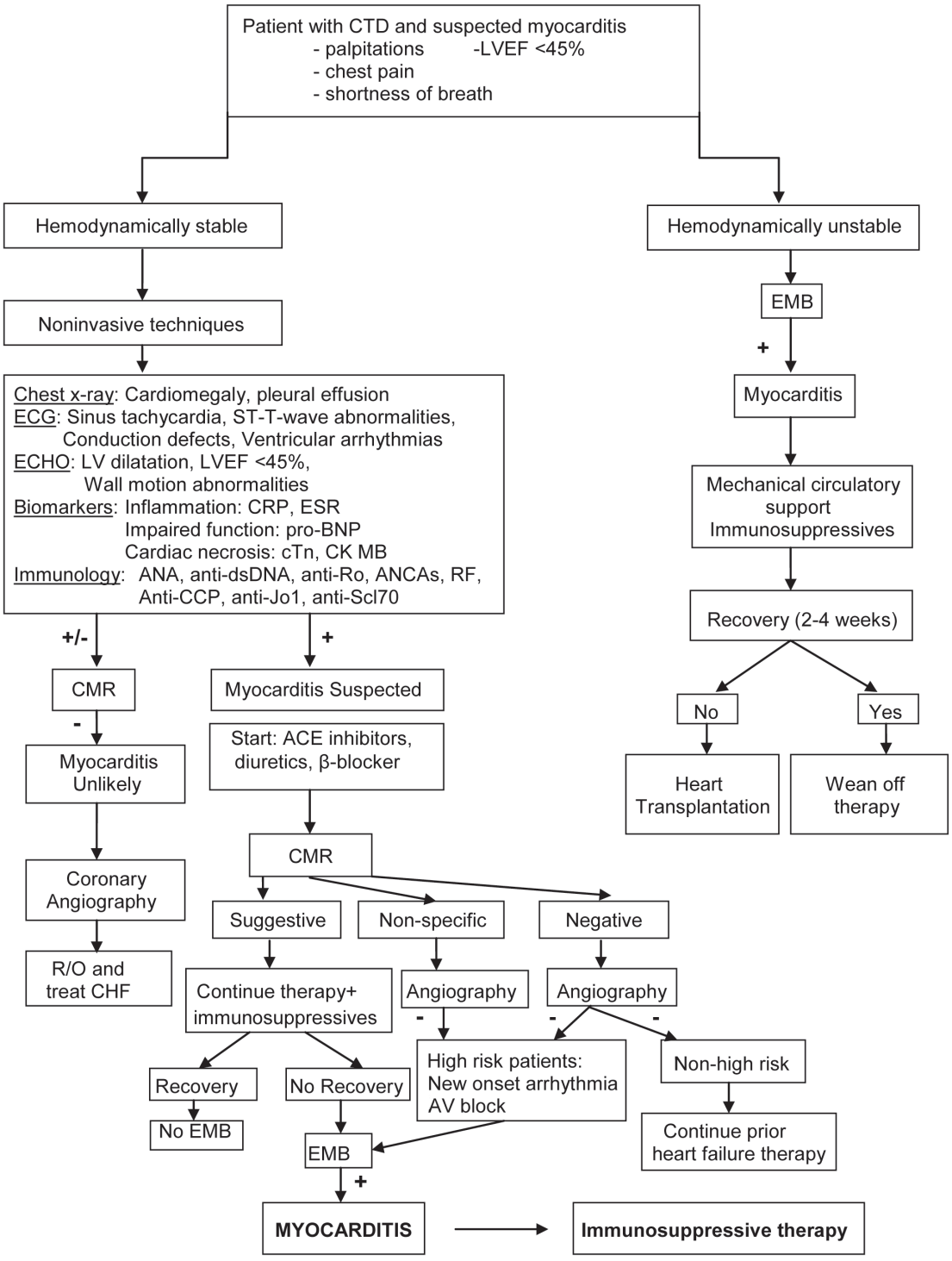

FIGURE 1. Diagnostic algorithm for diagnosing myocarditis in a patient with connective tissue disease (CTD). ACE = angiotensin converting enzyme; ANA = antinuclear antibodies; ANCA = anti-neutrophil cytoplasmic antibodies; AV = atrioventricular; BNP = brain natriuretic peptide; CCP = cyclic citrullinated peptide; CHF = congestive heart failure; CK MB = creatine kinase isoform MB; CMR = cardiac magnetic resonance; CRP = C-reactive protein; cTn = cardiac troponin(s); DNA = deoxyribonucleic acid; dsDNA = double stranded DNA; ECG = electrocardiogram; ECHO = echocardiography; EMB = endomyocardial biopsy; ESR = erythrocyte sedimentation rate; LV = left ventric-le(-ular); LVEF = left ventricular ejection fraction; RF = rheumatoid factor; R/O = rule out

supporting the theory that lupus myocarditis is an immune complex mediated vascular disorder.[21,22]

Myocarditis may present as fever, dyspnea, palpitations, non-exertional chest pain with resting tachycardia, jugular venous distention, peripheral edema and new onset cardiac murmurs.[23] Myocarditis should be suspected in patients who present with new onset arrhythmias (sinus tachycardia) or conduction defects.[6,23] Despite the fact that conduction defects are rare in adult patients with SLE, infants born to mothers with positive anti-Ro and anti-La antibodies have increased incidence of congenital complete AV block.[9] Probably myocardial inflammation and fibrosis of the conduction system is caused by the transplacental passage of these antibodies to the fetus.[6,9] Further studies should be done in order to prove if this antibody has a direct arrhythmogenic effect. If lupus myocarditis remains uncontrolled, progression to dilated cardiomyopathy and chronic heart failure may occur.[19]

The diagnosis of lupus myocarditis is based on clinical suspicion. The electrocardiogram reveals non-specific ST-T wave changes, conduction defects, premature atrial or ventricular beats and ventricular or supraventricular tachycardia.[24] There is echocardiographic evidence of segmental or global wall motion abnormality, accompanied by reduced LV systolic function (LV ejection fraction), pericardial effusion and pulmonary hypertension. Cardiac magnetic resonance (CMR) is a non invasive technique sensitive to changes that characterize lupus myocarditis.[25] CMR provides information about edema, increased capillary leakage and focal necrosis of cardiac muscle. Increased T2-weighted signal is a sensitive indicator of myocardial disease during the acute phase of inflammation, as a result of edema presence, even in the absence of clinically overt myocardial involvement.[14] Extensive subendocardial late gadolinium enhancement (LGE) images represent myocardial fibrosis, which is associated with chronic inflammation rather than active acute myocarditis.[14]

As there is no single treatment for SLE, appropriate therapy should be individualized and selected according with the severity of disease manifestations. Immunosuppressants may be introduced for treatment of lupus myocarditis, in order to improve systolic heart function. Severe forms of disease should be treated with intravenous pulses of methylprednisolone for three days, followed by intravenously or orally administrated prednisone (1 mg/kg/d) with gradual tapering. Other immunosuppressants, such as cyclophosphamide, azathioprine, mycophenolate mofetil, should also be added.[9,19] Some case reports revealed the beneficial role of intravenous gamma globulin usage in steroid-refractory lupus myocarditis cases.[26] Furthermore, supportive therapy for LV dysfunction, including angiotensin converting enzyme inhibitors, diuretics and β-adrenergic blocking agents, should be added in all patients.[19] During the follow up period, echocardiographic findings in most patients get improved, while a big percentage of patients show reversal of myocardial damage in a period of 6 months following immunomodulatory treatment.[27] Mortality rates are higher in clinically overt myocarditis than in the subclinical form. In general, development of myocarditis in SLE reflects worse overall disease activity.[23]

RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is a common autoimmune, inflammatory disorder that affects almost 1% of the adult population.[29] The disease has a female predominance and its peak onset is during their third to fifth decade of life.[9] RA typically presents with symmetrical polyarthritis of small and large joints, accompanied by variable in duration morning stiffness and by presence of autoantibodies particularly to rheumatoid factors and citrullinated peptides.[28] A positive rheumatoid factor does not confirm the diagnosis of RA, as it may be present in healthy individuals and in a variety of other diseases. The anti-cyclic citrullinated peptide test offers some specificity to the serologic diagnosis.[28] However, the RA diagnosis is based on clinical presentation. Seropositive RA patients present with more severe disease and extra-articular manifestations.

Myocarditis in RA is a rare complication, that seldom becomes clinically apparent.[9] Higher RA disease activity is associated with increased myocarditis incidence. Inflammatory infiltration of the myocardium and the conductive system is the main mechanism of developing myocarditis.[5] Two different histological patterns of RA myocarditis have been described. The non-specific form, which can also be observed in other disorders, is characterized by presence of an infiltrate that might be composed of lymphocytes, plasma cells, histiocytes and involves the collagenous interstitium of the heart. The granulomatous form is considered as the specific type for RA myocarditis. Granulomas are usually formed in seropositive RA patients, morphologically are identical to subcutaneous rheumatoid nodules and they usually appear in the left ventricle.[29] These two forms of RA myocarditis are implicated in the pathogenesis of arrhythmias, conduction disorders and secondary dilated cardiomyopathy resulting in heart failure with severe diastolic impairment.[9,29]

Symptoms of RA myocarditis are usually subtle, and when they become clinically apparent are associated with advanced heart failure. Clinical presentation of myocarditis includes fatigue, mild dyspnea or chest pain and palpitations. During early stages, myocarditis is undetectable with the everyday used imaging techniques, such as echocardiography or scintigraphy.[29] The electrocardiogram may show sinus tachycardia, T waves abnormalities and conduction defects.[7] Echocardiography in RA myocarditis reveals LV diastolic dysfunction, such as increased left atrial volume, enlarged left atria size, alternations in E/A wave ratio and elevated systolic pulmonary artery pressures.[30] CMR, is the ideal technique for diagnosis of myocarditis. T2-weighted images detect pres-

ence of edema, which is apparent when active inflammation is present. High levels of early myocardial enhancement after gadolinium administration are due to increased membrane permeability. Late gadolinium enhanced images detect myocardial necrosis occurring in RA.[29] The pattern of lesions is mainly intra-myocardial or subepicardial, can be found at any area of myocardium and is independent of the distribution of coronary vessels. Finally, CMR offers the opportunity to detect silent (subclinical) myocardial involvement in RA patient.[31]

In general, higher disease activity, long lasting disease and extra-articular manifestations are strongly associated with increased myocarditis incidence.[29] Because of the rarity of rheumatoid myocarditis, optimal treatment is uncertain. As initial therapy, usage of high dose methylprednisolone (pulse therapy 500-1000 mg/day for 3 days, or 80 mg/day) is usually suggested. Reduction of RA systemic manifestations, including myocarditis, is evaluated by early introduction of therapy with disease modifying drugs. Traditional disease-modifying antirheumatic drugs that may be used as monotherapy or in combination are methotrexate (up to 25 mg/week), sulfasalazine (up to 3 g/day), leflunomide (20 mg/day) and hydroxychloroquine (400 mg/day). Aggressive control of systemic inflammation of RA with methotrexate or anti-tumor necrosis factor (TNF) agents may reduce cardiovascular morbidity.[9] Recent studies showed that treatment with anti-TNF agents or interleucin-6 inhibition agents led to improvement of diastolic function within a follow-up period of 6-12 months.[32] However, administration of anti-TNF agents in patients with severe heart failure (New York Heart Association functional class III-IV) should be avoided because of increased cardiac mortality.[33] Supportive treatment for improvement of LV dysfunction caused by RA myocarditis, such as angiotensin converting enzyme inhibitors, or angiotensin-receptor blockers, diuretics and β-adrenergic blocking agents, is commonly suggested.[29]

SYSTEMIC SCLEROSIS

Systemic sclerosis or systemic scleroderma (SSc) is a CTD characterized by microangiopathy and tissue fibrosis.[34] Involvement of vascular system results in development of Raynaud's phenomenon early in the disease course. Deposition and overproduction of extracellular matrix proteins and collagen result in tissue fibrosis and dysfunction. Several growth factors such as transforming or tumor growth factor (TGF)-β and endothelin-1 are involved in tissue remodeling, whereas vasospasm causes repeated focal ischemia.[5] Systemic scleroderma is a rare disease, with incidence 0.6 to 19 per million of general population per year. Disease has a female predominance and occurs between 45 and 65 years of life. It is divided into limited cutaneous and diffuse/systemic form. Almost all patients with SSc or CREST (calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia) syndrome have positive ANA, while anti-topoisomerase antibodies (anti-SCL 70) may be also positive in SSc patients.[9]

SSc patients with long lasting Raynaud phenomenon, coexisting myositis and positive anti-ribonucleoprotein antibodies are more prone to develop myocarditis, which usually has a subclinical course and sometimes can be underestimated.[1] When clinically apparent, primary myocardial involvement is considered as an important prognostic factor for disease outcome.[38] Multiple causes can lead to myocarditis pathogenesis. Myocardial damage in SSc is much more common in patients with diffuse disease and/or coexisting peripheral skeletal myositis.[9] A mild but persistent increase in creatine kinase-MB and/or troponin levels refers to possible myocarditis. Besides skeletal myositis, pericardial effusion should always be counted as a red flag for identification of myocardial inflammation.[39] Additional factors, such as early disease, ventricular ectopic beats, wall motion abnormalities, ANCA positivity, myositis and pericardial effusion should be evaluated. ANCA antibodies are uncommon in SSc, however a correlation between C-ANCA/PR3 positivity and SSc myocarditis was found in some studies.[40]

Myocardial biopsy may increase the frequency of detection of myocarditis. However, the procedure is rarely indicated because of its invasive nature and high rate of sampling errors.[41] Myocardial biopsies show fibrotic changes in endocardial and subendocardial layer, severe interstitial fibrosis, proliferating myofibroblasts and patchy infiltrations composed of macrophages and activated T-helper lymphocytes.[9,36] Clinical presentation of myocarditis in SSc may include chest pain, palpitations, shortness of breath and signs of heart failure unrelated to lung disease progression. Conduction defects are frequently observed in the electrocardiogram of asymptomatic patients.[6] Premature ventricular contractions and monomorphic tachycardias are the most common arrhythmias in SSc.[37] Clinically overt SSc myocarditis makes prognosis worse and leads to sudden death.[6,9] Coexistent peripheral skeletal myositis is associated with increased risk for heart failure and mortality.

The electrocardiographic findings of SSc myocarditis include supraventricular tachycardia, conduction defects and ST-segment abnormalities.[35,36] Echocardiography, shows segmental or global LV dysfunction, decreased ejection fraction, diastolic and systolic dysfunction with E/A ratio <1 and sometimes pericardial effusion.[36,38] Angiographic studies reveal normal coronary arteries, supporting the theory of impaired microvasculature in the pathogenesis of myocarditis in SSc.[9,36]

Cardiac magnetic resonance is a useful modality for accurately detecting fibrotic myocardium in SSc. Late gadolinium enhancement imaging can identify myocardial fibrosis in 66% of SSc patients.[37] Myocardial fibrosis has a linear pattern and is limited to the midwall layer, with invariable sparing of the subendocardium and epicardium.[37] It has a non-coronary distribution, predominantly located in the basal and midcavity

segments of the left ventricle. Increased signal T2-weighted images, are also observed in SSc myocarditis cases.[35] CMR also provides the means for monitoring the effects of treatment and thus prevents deterioration of heart disease. Several studies revealed an association between arrhythmias and degree of fibrosis.[6] However, myocardial fibrosis detected by CMR may occur concurrently or independently of fibrosis of other internal organs and may not be associated with the extent of skin involvement.[42]

Recognition of myocarditis determines the therapeutic implications. The goal of immunosuppression is clinical improvement, normalization of cardiac enzymes and CMR stabilization. Best therapeutic results are obtained in patients with lower degrees of fibrosis.[36] To date there is no proven effective therapy that can limit the progression of SSc, and the target remains to control the symptoms. Long-term high doses of glucocorticoids should be cautiously used because they do not control heart failure and they increase the risk of developing scleroderma renal crisis.[9] We usually administer 0.5 mg/kg/day of prednisone, followed by 5-mg dose tapering every 10 days, while the lowest possible effective dose that should be used remains preferably below 20 mg/day. Corticosteroids may control the inflammatory process but not the subsequent heart failure.[43]

Further immunomodulatory treatment includes cyclophosphamide (2 mg/kg/day up to cumulative dose of 6 g), followed by azathioprine (2 mg/kg/day). In refractory cases rituximab in combination with cyclophosphamide has been tried and further deterioration of cardiac function was prevented.[35] Patients progressing to heart failure should be also controlled with diuretics, angiotensin converting enzyme inhibitors and aspirin (100 mg/day). Amiodarone controls ventricular arrhythmias.[9] Vasodilatory therapy with calcium-channel blockers, prostacycline or endothelin antagonist may be associated with improvement in intimal proliferation.

Myocarditis is a major predictor of increased mortality in SSc, hence early diagnosis and induction therapy is crucial for modifying the disease course, by leading to significant clinical improvement, normalization of cardiac enzymes and regression or stabilization of CMR in the majority of cases.[36,37]

INFLAMMATORY MYOPATHIES

Autoimmune inflammatory myopathies (IM), namely dermatomyositis (DM) and polymyositis (PM) are chronic inflammatory muscle diseases that share common clinical features, such as proximal muscle weakness, elevated levels of muscle enzymes, electromyographic alterations, presence of autoantibodies, histopathological evidence of inflammatory infiltrations in skeletal muscles and extramuscular manifestations.[44] Extramuscular involvement, such as the skin in DM, interstitial lung disease, arthritis, gastrointestinal involvement (dysphagia), Raynaud phenomenon and photosensitivity, is common. DM is associated with skin involvement (heliotrope rash, Gottron's papules and sign). Both entities are associated with increased incidence of neoplasms. When extramuscular manifestations, such as interstitial lung disease and cardiac involvement are present, the survival prognosis is getting worse.[46] Despite clinical similarities, certain histopathological findings help to distinguish these disorders from each other and reflect their distinct pathophysiologic pathways.

Autoantibodies are frequently detected in patients with inflammatory myopathies. Antinuclear antibodies may be present in 80% of patients with DM or PM. Antisynthetase antibodies are myositis specific antibodies. The most frequently observed is anti-Jo1 antibody, which is directed against histidyl-tRNA synthetase and is seen in about 20% of patients with idiopathic inflammatory myositis.[47] Anti-Jo1 antibodies are strongly associated with several clinical findings, including interstitial lung disease, Raynaud's phenomenon, arthritis and mechanic hands. Other myositis specific antibodies, but less commonly detected, are anti-Mi-2 and anti-signal-recognition peptide autoantibodies.[48]

Myocarditis in IM is caused by direct inflammation of the heart muscle.[5] The incidence of clinical myocardial involvement in these conditions is rather low.[44] Myocarditis usually occurs simultaneously with skeletal muscle inflammation, but it may also develop even in patients with low disease activity. Histopathological findings resemble those of skeletal muscle inflammation. Infiltrations are composed of mononuclear inflammatory cells, localized in the endomysium and the perivascular areas with degeneration of cardiomyocytes.[49] Similar histopathological findings are also observed in the conducting system, including lymphocytic infiltrates, fibrosis of sinoatrial node and contraction band necrosis.[45]

The symptomatic form of cardiac involvement with histologic evidence of myocarditis in IM, including clinically evident congestive heart failure with impaired LV function, is relatively uncommon.[45] Other clinical symptoms, such as palpitations, shortness of breath, non-productive cough, chest pain and syncope have been described. Physical examination may reveal signs of jugular venous distention, wheezing, rhonchi at the lower lung fields and peripheral edema. Techniques such as electrocardiography (ECG), Holter monitoring, echocardiography, myocardial scintigraphy have poor sensitivity and specificity for detecting subclinical heart abnormalities.[44] Arrhythmias and conduction defects detected by electrocardiographic studies are frequently reported. Atrial and ventricular arrhythmias, bundle branch block, AV block, atrial and ventricular premature beats, abnormal Q waves and non specific ST-T wave changes can be found in ECG and Holter monitoring.[44]

Echocardiography reveals segmental or global hypokinesia, septal and LV hypertrophy resulting in diastolic dysfunction.[50] Nuclear imaging techniques lack sensitivity and specificity

for detecting myocarditis in IM. CMR LGE imaging proved more sensitive to detect affected parts of the myocardium in inflammatory myopathies than conventional laboratory tests (creatine kinase, C-reactive protein, erythrocyte sedimentation rate, cardiac troponins).[51] Increased LGE intensity signal is usually observed in the left ventricle. LGE imaging is also sensitive in detecting changes of myocardium following immunomodulatory therapy.[7] Cardiac troponins are a reliable marker with highest specificity for detection of myocardial involvement in patients with inflammatory myocardial damage,[45] compared to creatinine kinase isoenzyme MB.[44]

Treatment of myocarditis in IM is usually empirical. The effects of glucocorticoids and immunosuppressants on cardiac manifestations are conflicting, since some cases of congestive heart failure get improved and some others deteriorate. Some studies revealed that myocarditis occurrence is independent of steroid therapy and disease activity.[49] There are some case reports suggesting that rituximab has good results in management of myocarditis.[52] Besides immunosuppressive therapy, patients experiencing symptoms of congestive heart failure, should be treated with medications such as nitrates, β-blockers, angiotensin converting enzyme inhibitors and diuretics. There are few reports of patients with complete heart block that have been treated with a pacemaker, and fewer reports of patients successfully transplanted for dilated cardiomyopathy.[45]

SYSTEMIC VASCULITIDES

CHURG STRAUSS SYNDROME/EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS (EGPA)

Primary systemic vasculitides are inflammatory necrotizing diseases of unknown etiology, whose differentiation depends upon the vessel size and the organ affected. Churg Strauss syndrome (CSS) is a rare systemic vasculitis of small and medium - sized vessels, frequently involving the lung, skin, peripheral nerves, kidneys, heart and is associated with peripheral eosinophilia (>10% eosinophils).[53] EGPA occurs primarily in patients with a previous history of allergic rhinitis and adult onset asthma (>95% of cases). The incidence of EGPA is approximately 2.4 cases/1000000 persons, it may affect any age and gender. In general, the prognosis of EGPA is good, with overall 10-year survival rate of 81-92%.

Clinical features of EGPA typically develop in three phases that may appear simultaneously. The prodromal phase consists of asthma and allergic manifestations. The second phase is characterized by peripheral blood and tissue eosinophilia in the lungs and the myocardium and finally the systemic phase, which is accompanied by life – threatening necrotizing vasculitis. Involvement of the myocardium has been described in the third phase as a vasculitic lesion in heart tissue.[57] EGPA is diagnosed on the basis of clinical and histopathological features. ANCA antibodies are found in 40-60% of patients with CSS. These are directed against myeloperoxidase with perinuclear staining pattern.[57] ANCA – positive patients experience neurologic and renal manifestations, while cardiac involvement has been associated with absence of ANCA antibodies.[59]

Eosinophilic myocarditis is one of the most common forms of cardiac involvement in patients with CSS.[54] Eosinophilic myocarditis may be clinically expressed as acute myocardial infarction, accompanied by ECG changes, elevated levels of cardiac enzymes (creatine kinase MB, troponin), hypertrophy of left ventricle in echocardiography, while coronary angiography excludes acute myocardial infarction. The differential diagnosis of eosinophilic myocarditis includes other types of myocarditis that are characterized by myocardial eosinophilic infiltration and may occur in the course of hypereosinophilic syndromes. Myocardial damage occurs more often by direct eosinophilic infiltration, resulting in fibrosis and less often it follows the model of systemic vasculitis.[54] In some cases, myocardial granulomas are also observed.[9] Myocardial involvement is an important prognostic factor in the "five factor score" for EGPA, associated with increased rates of mortality, so early diagnosis is of great clinical importance.[56]

Unfortunately due to its subclinical course, myocarditis might be underdiagnosed. However, when it is clinically apparent, symptoms such as chest pain, shortness of breath and palpitations may be present. Myocarditis seems to be highly prevalent among EGPA patients in remission, so an adequate evaluation plan should be designed in order to eliminate irreversible changes by inducing appropriate therapy.[57] Electrocardiographic changes include right or left bundle branch block, ST–T waves abnormalities, ventricular arrhythmias, pathologic Q waves and conduction defects.[57] Pericardial effusion, wall motion abnormalities, valvular insufficiency due to fibrosis, LV diastolic dysfunction and/or impaired systolic function are findings of echocardiography. Diastolic dysfunction can be related to increased myocardial stiffness caused by inflammatory process and fibrotic lesions.[56]

Coronary angiography is usually normal, suggesting predominant involvement of smaller vessels in EGPA myocarditis.[54,57] Cardiac magnetic resonance has been successfully used for the evaluation of myocardial inflammation, even in subclinical forms of disease with low inflammatory indexes. The typical CMR pattern includes patchy myocardial edema that may be smaller than myocardial scarring.[60] Scar has the form of diffuse subendocardial LGE, while an epicardial and intramyocardial pattern can be also present.[7,59] The patients with higher number of segments affected on LGE usually demonstrate a decreased LV ejection fraction (<50%), positive ECG stress test and ventricular arrhythmias on Holter monitoring.[56] Signs of acute ongoing inflammation, such as edema with increased T2 weighted imaging, hyperemia and increased capillary leakage detected by early gadolinium enhancement can be present.[56,59] Peak eosinophilia, before the initiation of corticosteroid therapy is associated with presence

of systolic heart failure and rhythm disturbances. In EGPA ANCA antibodies correlate negatively with heart involvement. Elevated levels of cardiac enzymes are also observed.

Early diagnosis of myocarditis in EGPA and selection of appropriate therapy can prevent progression and improve prognosis. Acute onset disease should be treated with intravenous pulses of glucocorticoids (methylprednisolone 1 g/day for 3 days) followed by oral glucocorticoid therapy.[55] Administration of prednisone (0.5-1 mg/kg/day) is required until clinical remission is obtained.[54] Gradual tapering of corticosteroids to the lowest dose is required for control of symptoms and signs of active disease. Further addition of immunosuppressive therapy is recommended for EGPA myocarditis, in order to achieve lower mortality rates. Cyclophosphamide can be administered orally every day or intravenously every month, for 6 to12 months. Different studies revealed that more episodes of myocarditis relapse occurred when 6 pulses of cyclophosphamide were used in contrast to 12 pulses. [55] Azathioprine is further used as maintenance therapy.[59] In general, immediate therapy allows recovery of cardiac function and reduces mortality associated with EGPA.[55]

WEGENER GRANULOMATOSIS/ GRANULOMATOSIS WITH POLYANGIITIS (GPA)

Wegener granulomatosis is a multisystem disease of unknown etiology, characterized by granulomatous inflammation, tissue necrosis and variable degrees of vasculitis in small and medium – sized blood vessels. Although GPA may affect any organ system, the disease has a predilection for the upper respiratory tract, lungs and kidneys.[61] The renal manifestation, a pauci – immune glomerulonephritis, is often associated with rapidly progressive renal dysfunction. Wegener granulomatosis can be generalized when all three major anatomic sites are affected and limited in the absence of renal involvement. The annual incidence of GPA is at least 8.5 cases per million of people, males and females are equally affected and the mean age of diagnosis is the fourth decade of life.

The majority of GPA cases and particularly those with severe widespread disease are strongly associated with the presence of cytoplasmic anti-neutrophil cytoplasmic antibodies (c-ANCA) with specificity against proteinase-3 (anti-PR3).[62] Only 10% of patients with GPA have positive perinuclear (p)-ANCA, with anti-myeloperoxidase pattern, while 10-20% of patients with active – untreated GPA are ANCA negative, suggesting that a negative ANCA assay does not preclude the diagnosis of GPA.[64] Overall, ANCA titers correlate with GPA activity in 60% of cases. A rise in ANCA titer or a transition from negative to positive in patients with clinically inactive GPA heralds exacerbation of disease.[58]

Although clinically overt myocarditis in GPA is rare, there is growing evidence of subclinical myocardial involvement during the course of the disease, associated with poor prognosis. Myocardial involvement is usually caused by inflammatory infiltration of cardiomyocyte and vessel wall, progressing to cardiomyopathy with impaired diastolic function.[62] High prevalence of myocarditis reflects increased disease activity and resistance to therapy, and it is recognized as a predictor of relapse. Clinical presentation ranges from mild dyspnea, chest pain and palpitations to sudden death with new onset supraventricular arrhythmias and complete heart block.[63] Endomyocardial biopsy, used for diagnosis of GPA myocarditis, has a poor diagnostic accuracy due to patchy myocardial involvement.[62]

The electrocardiogram and echocardiography are the most often used screening tools for evaluation of myocardial involvement in GPA. In the subclinical form, the above techniques can be normal. The ECG may show sinus tachycardia, ventricular arrhythmias and conduction defects.[58] Echocardiography may reveal diastolic dysfunction with segmental wall abnormalities, LV dilatation and decreased LV ejection fraction (<50%).[58,62] CMR appears to be a sensitive noninvasive diagnostic technique to assess myocardial involvement in GPA, even in the subclinical form of the disease. Combination of T2 - weighted and LGE images can define the presence, acuity and extent of myocardial involvement in course of GPA, by distinguishing acute from chronic inflammation. T2 - weighted images detect myocardial edema, which corresponds to acute inflammation phase, and LGE images detect fibrosis. Most of lesions detected by CMR - LGE imaging are located in the left ventricle and are usually distributed as patchy lesions in all myocardial layers (subendocardial, midwall, subepicardial).[58]

Treatment for myocarditis should be individualized according to GPA disease activity and severity. Common regimens used are intravenous pulses of methylprednisolone, followed by daily prednisone (1 mg/kg/day) and subsequent tapering with goal to reach 10 mg/day. Cyclophosphamide is administered in dose of 1.5 mg/kg/day every 4 weeks for 6 months.[59,62] Azathioprine can be used as a maintenance therapy in dose of 2 mg/kg daily.[62] When the above regimens fail to achieve disease control or relapses occur, rituximab should be used. The efficacy and safety effect of rituximab is similar to that of cyclophosphamide.[65] Several studies have demonstrated regression of myocarditis CMR findings after treatment with corticosteroids, cyclophosphamide and rituximab.[66]

SARCOIDOSIS

Sarcoidosis is a rare systemic, non-caseating granulomatous disease of unknown etiology that classically involves lungs, but can affect any organ within the body, including the heart.[67] Sarcoidosis typically affects young people. An antigen – driven cell mediated immune response is thought to be implicated in disease pathogenesis. Antigens processed by antigen presenting cells, bear human leucocyte antigen (HLA) class II, that are then recognized by CD4 + T cells, leading to an augmented immune response, persistent inflammation, non-caseating granuloma formation, potential fibrosis of involved organs

and variations in clinical presentation and severity of illness. Sarcoidosis may typically present with one or more of the following abnormalities, such as bilateral hilar adenopathy, pulmonary reticular opacities, skin, joint and eye lesions.

Cardiac sarcoidosis can be a benign, incidentally discovered condition or a life threatening disorder. Several autopsy studies established an incidence of myocardial involvement in 20 to 50% of cases, while only a small proportion of them (5%) become symptomatic, influencing the prognosis and mortality rates.[67] Inflammatory infiltration of myocardium is the main mechanism leading to sarcoid myocarditis.[69] Sarcoid myocarditis may be detected alone, may precede, follow or occur concurrently with other organ involvement, for example lung involvement. Endomyocardial biopsy is essential for diagnosis of sarcoid myocarditis. However, the procedure has limited sensitivity because of its invasive nature and the high rate of false negative results secondary to patchy distribution of myocardial infiltrartion.[70] Histology reveals small non-caseating granulomas with extensive fibrosis and segmental myocardial distribution.[68] Myocardial granulomas predominantly affect the basal and lateral LV septum, papillary muscles and right atrium.[70]

The signs and symptoms of sarcoid myocarditis depend upon the location and extent of granulomatous inflammation. Sarcoid myocarditis usually presents with conduction abnormalities, ventricular and atrial arrhythmias, pericardial effusion and can progress to refractory congestive heart failure and sudden death.[67] Complete heart block is the most common finding in patients with clinically evident cardiac sarcoidosis.[68] Heart failure with diastolic and systolic dysfunction can occur when there is extensive granulomatous infiltration of myocardium. The diagnosis is a great challenge, frequently missed or delayed, especially when the disease remains asymptomatic. The electrocardiogram detects arrhythmias, conduction defects or repolarization abnormalities, such as premature ventricular beats, ventricular tachycardia, right bundle branch block, axis deviation or AV block.[68]

Echocardiographic findings include abnormalities such as LV dilatation, septal thinning, segmental or global hypokinesia of the left ventricle, ventricular aneurysms (usually apical), valvular regurgitation, mitral valve prolapse secondary to papillary muscle dysfunction, and/or right ventricular dilatation and hypokinesis.[71] Sarcoid lesions may also cause an increase in myocardial wall thickness, simulating LV hypertrophy, or increased interventricular septal thickness, resembling hypertrophic cardiomyopathy. The regional wall motion abnormalities are independent of coronary vessel distribution.

Cardiac magnetic resonance is the technique of choice in the evaluation of sarcoid myocarditis, as it enables a noninvasive and accurate diagnosis. Increased T2-weighted signal intensity and early gadolinium enhancement imaging detect edema, a sign of acute inflammation.[69] T1-weighted images illustrate wall motion abnormalities, hypertrophy due to possible infiltrative disease, wall thinning or heart failure. LGE imaging assesses fibrosis or scar and represents chronic phase of disease. In case of sarcoid myocarditis, LGE shows diffuse or focal enhancement in the mid-myocardial or subepicardial region independently of coronary vessel distribution.[7,72] Different studies revealed that CMR LGE imaging has a prognostic value for sarcoid myocarditis, by providing information for future potential lethal events including death.[5,72] Coronary angiography is usually normal, as sarcoidosis, rarely involves coronary vessels. Typical presentation with complete heart block, elevated serum angiotensin converting enzyme and typical histologic and CMR findings are crucial for the diagnosis of myocarditis.

Treatment of sarcoid myocarditis aims to control the inflammation, prevent fibrosis and further compromise of cardiac structure or function. Patients usually respond well to steroids, rather than to therapy for acute heart failure. Steroids are capable of slowing the progression of inflammation and fibrosis and of preventing further LV function deterioration.[69,73] The optimal dose of corticosteroids is not known. Several cohort studies have shown benefits of oral prednisone at doses 30-60 mg/day for 8-12 weeks with gradual tapering to the dose of 10-20 mg/day over 6 months.[73] Glucocorticoid treatment should be continued for at least one to two years, and dosage should always be adjusted because of side effects. Relapses of sarcoid myocarditis should be handled by reinstituting prednisone at 30-60 mg/day. Patients that cannot respond to glucocorticoids or cannot tolerate the drug because of side effects, alternative agents such as hydroxychloroquine or cyclosporine may be used, depending on patient and disease severity. Since incidence of sudden death due to ventricular tachyarrhythmias or conduction defects is high, an implantable cardioverter defibrillator is sometimes recommended.[74] Patients with symptomatic sarcoid myocarditis and coexisting pulmonary involvement have decreased overall survival.

CONCLUSION

Myocardial involvement in autoimmune rheumatic diseases is the consequence of various pathologic alterations in immune processes that result in impaired heart contractility or conduction system disease. Prompt diagnosis of myocarditis is of great importance for the selection of proper immunosuppression therapy, so that reversal of myocardial dysfunction can be achieved. Cooperation among rheumatologists and cardiologists is required for a better disease outcome.

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