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Review article

Cardiovascular involvement in systemic rheumatic diseases: An integrated view for the treating physicians

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ABSTRACT

Systemic autoimmune diseases can affect various kinds of organs including the kidney, the skin, soft tissue and the bone. Among others, cardiovascular involvement in rheumatic diseases has been shown to affect myocardium, pericardium, cardiac vessels, conduction system and valves, eventually leading to increased mortality. In general, underlying chronic inflammation leads to premature atherosclerosis, but also other manifestations such as arrhythmia and heart failure may have a 'silent' progress. Traditional cardiovascular risk factors play a secondary role, while disease-specific factors (i.e. disease duration, severity, antibody positivity, persistent disease activity) can directly influence the cardiovascular system. Therefore, early diagnosis is critical to optimize management and to control inflammatory activity and recent data suggest that risk factors (i.e. hypercholesterolemia and hypertension) need intensive treatment as well. With the advent of immunosuppressive agents, most rheumatic diseases are well controlled on treatment, but information related to their cardioprotective efficacy is not well-defined. In this review, we focus on cardiovascular involvement in rheumatic diseases and highlight current evidence which should be of help for the treating physicians. Moreover, cardiotoxicity of immunosuppressive drugs is a rare issue and such potential adverse events will be briefly discussed.

Contents

Abbreviations: SLE, systemic lupus erythematosus; RA, rheumatoid arthritis; C3, complement factor 3; IgM, IgG, IgA immunoglobulin M, G, A; APS, antiphospholipid syndrome; anti-Ro/SSA, anti-Sjögren syndrome-related antigen A; HF, heart failure; CVD, cardiovascular disease; CIMT, carotid intima-media thickness; HDLc, high-density lipoprotein cholesterol; TG, triglyceride; ESR, erythrocyte sedimentation rate; SLEDAI, systemic lupus erythematosus disease activity index; ACE, angiotensin converting enzyme; LDLc, low-density lipoprotein cholesterol; MI, myocardial infarction; AMI, acute myocardial infarction; PCI, percutaneous coronary intervention; QTc, corrected QT; CQ, chloroquine; AV, atrioventricular; PE, pericardial effusion; RF, rheumatoid factor; CAD, coronary artery disease; IHD, ischemic heart disease; FMD, flow-mediated dilation; anti-CCP, anti-cyclic citrullinated peptide; DAS28, disease activity score in 28 joints; CRP, C-reactive protein; ACS, acute coronary syndrome; CHF, congestive heart failure; IL, interleukin; LV, left ventricle; AF, atrial fibrillation; SCD, sudden cardiac death; ANS, autonomic nervous system; TNF- α, tumor necrosis factor- α; dc/lcSSc, diffuse cutaneous/limited cutaneous systemic sclerosis; CFR, coronary flow reserve; ANA, anti-nuclear antibody; ACA, anti-centromere antibody; Scl-70, anti-topoisomerase I antibody; RBBB, right bundle branch block; HRV, heart rate variability; HRT, heart rate turbulence; GCA, giant cell arteritis; TAK, Takayasu's arteritis; NT-pro BNP, N-terminal pro b-type natriuretic peptide; CVE, cardiovascular event; CABG, coronary artery bypass grafting; KD, Kawasaki disease; WBC, white blood cell; cTnI, coronary troponin I; IVIG, intravenous immunoglobulin; ANCA, anti-neutrophil cytoplasmic antibody; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; EGPA, eosinophilic granulomatosis with polyangiitis; HSP, Henoch-Schönlein purpura; BD, Behcet's disease; PSS, primary Sjögren syndrome; AS, ankylosing spondylitis; NSAID, non-steroidal anti-inflammatory drug; IIM, idiopathic inflammatory myopathy; DMARD, disease-modifying anti-rheumatic drug; MTX, methotrexate.

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1. Introduction

Autoimmune rheumatic diseases are characterized by inflammation of a single or multiple organs. Typically, rheumatic diseases include systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), systemic sclerosis, vasculitis, Sjögren's syndrome, Behcet's disease and axial spondyloarthritis. Manifestations of these diseases vary widely and some are characterized by a certain pattern of organ involvement, for example, Behcet's disease is often associated with oral, skin and ocular lesions.

The prevalence of cardiovascular involvement in rheumatic disorders has been underestimated for a long time. However, advances in the therapeutic arsenal and the longer life expectancy of these patients led to a closer look “behind-the-scene” complications of rheumatic diseases. Bearing in mind that sudden death cases have been reported in various rheumatic diseases, it is tempting to speculate that cardiovascular causes are mostly responsible for these fatalities.

Cardiovascular involvement in systemic rheumatic diseases usually presents subclinical without fatal clinical features. However, in the long term, the accumulation of damage may culminate in life-threatening complications. Therefore, it is essential to keep in mind the risk of cardiovascular manifestations and early diagnosis to prevent damage accrual with non-invasive diagnostic modalities is highly warranted.

In this review, we highlight that most cardiovascular complications are restricted to the pericardium, myocardium, valves, (premature) atherosclerosis, ischemia and conduction abnormality. We thoroughly discuss the prevalence and the characteristics of cardiovascular involvement in rheumatic diseases and describe the potential cardiotoxicity of anti-rheumatic drugs.

2. Systemic lupus erythematosus

2.1. Pericardial involvement

Pericarditis is the most frequent cardiac complication observed in patients with SLE. Pericarditis is associated with pericardial effusion (PE) in SLE patients. The prevalence of pericarditis and subsequent PE assessed by echocardiography varies from 9 to 54% [253]. In general, patients are asymptomatic and only a small amount of pericardial fluid is detected. 10 to 20% of SLE-induced pericarditis is known to progress to cardiac tamponade [254], which is treated with high doses of corticosteroids, followed by pericardiocentesis if needed. Although recurrent pericarditis is an intricate problem, several cases were reported for successfully treating recurrent pericarditis with colchicine and other measures [1, 2].

Risk factors for development of tamponade in pericarditis are not well-defined. In a study of 41 SLE patients with 9 tamponades, researchers claimed that males were more likely to present with pericarditis, while females progressed to tamponade more frequently. In addition, low C3 levels, anemia and renal disease are consistent findings in patients with pericarditis [3, 4]. In contrast, the volume of PE was not a significant risk factor of tamponade, since a wide range of effusion volume from 225 to 1700 ml was noted in tamponades [5].

2.2. Valve involvement

There are four spectrums of valve involvement observed in SLE: thickening, stenosis, regurgitation and vegetation [6]. The prevalence varies from 10 to 25% of affected patients. In detail, valve stenosis and regurgitation occur in 2 to 5% of SLE patients [7]. In addition, non-

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