EVALUATION OF CORONARY ARTERY DISEASE IN SYSTEMIC LUPUS ERYTHEMATOSUS AND SCLERODERMA: CORRELATION WITH PULMONARY HPERTENSION AND DISEASE ACTIVITY

Thesis Submitted for Partial Fulfillment of M.D. Degree in Rheumatology and Rehabilitation

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Abstract

***Objective*:** we aimed to detect the coronary artery disease in patients with systemic lupus erythematosus and scleroderma associated with pulmonary hypertension and its relation to disease activity.

Methods: Twenty patients with systemic lupus erythematosus (10 with pulmonary hypertension, and another 10 with normal pulmonary artery pressure), and 20 patients with sclerderma (10 with pulmonary hypertension, and another 10 with normal pulmonary artery pressure) were included in this study. Stress technetium 99m myocardial perfusion imaging was done for all patients. Patients with positive scinigraphic study were subjected to coronary angiography to exclude coronary artery lesion.

Results: Myocardial perfusion SPECT with a stress-rest protocol revealed that 7 patients had coronary artery disease, 3 (15%) patients with SLE and PH, 3 (15%) patients with scleroderma with PH, 1 (5%) patient with SLE with normal pulmonary artery pressure. There was high incidence of positive myocardial perfusion defects among SLE and SSc patients with pulmonary hypertension than those without. Coronary angiography revealed that only 1 sclerodrma patient with positive myocardial perfusion defect had coronary artery stenosis.

Conclusion: Coronary artery disease is a common association with SLE and SSc patients especially those with pulmonary hypertension. It is important to determine the presence of subclinical coronary artery disease in patients with SLE.

Keywords: Systemic lupus erythematosus- Scleroderma- Pulmonary hypertension- Coronary artery disease- Stress technetium 99m- Coronary angiography

AIM OF THE WORK

The objectives of this study are, the evaluation of coronary artery disease in patients with systemic lupus erythematosus and scleroderma associated with pulmonary hypertension and its relation to clinical parameters.

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List of abbreviations

- ACE: Angiotensin converting enzyme
- ACLs: Anticardiolipin antibodies
- ACR: American College of Rheumatology
- Alanine transaminase
- ALP: Alkaline phosphatase
- ANA: Antinuclear antibody
- Anti-ds DNA: Anti-double stranded deoxyribonucleic acid
- APLs: Antiphospholipid antibodies
- ARDS: Adult respiratory distress syndrome
- AST: Aspartate transaminase
- AT: atherosclerosis
- BAL: Bronchalveolar lavage
- BAL: Bronchalveolar lavage
- C3: Complement component 3
- C4: Complement component 4
- CAD: Coronary artery disease
- CBC: Complete blood picture
- CHD: Coronary heart disease
- CK: Creatine kinase
- CREST: Calcinosis, Raynaud's phenomenon, Esophageal dysmotility, Sclerodactly, telangectasia
- CRP: C-Reactive Protein
- CT: Computed tomography
- CTDs: Connective tissue diseases
- CVA: Cerebrovascular accident
- DLCO: Diffusion capacity for carbon monoxide
- DNA: Deoxyribonucleic acid antibody
- ECG: Electrocardiography
- ERAs: Endothelin-receptor antagonists
- ESR: Erythrocyte sedimentation rate
- ET-1: Endothelin-1
- FEF: Forced expiratory flow
- FEV: Forced expiratory volume
- Hb: Hemoglobin
- HRCT: High resolution computed tomography
- ILD: Interstitial lung disease
- INF-α: Interferon alpha
- INF-β: Interferon beta
- INF-γ: Interferon gamma

- IVIG: Intravenous immunoglobulin
- LA: Lupus anticoagulant
- LDH: Lactate dehydrogenase
- LDL: Low density lipoprotein
- MI: Myocardial infarction
- MMF: Mycophenolate mofetil
- MPI: Myocardial performance index
- NO: Nitric oxide
- NSAIDs: Non-steroidal anti-inflammatory drugs
- NYHA: New York Health Association
- OxLDL: Oxidized low density lipoprotein
- PASP: Pulmonary artery systolic pressure
- PGI2: Prostocyclin
- PH: Pulmonary hypertension
- RA: Rheumatoid arthritis
- RNA: Ribonucleic acid
- RNP: Ribonucleoprotein
- Scl-70: Scleroderma-70
- SLE: Systemic lupus erythematosus
- SLEDAI: Systemic lupus erythematosus disease activity index
- SPECT: Single photon emission computed tomography
- SRC: Scleroderma renal crises
- SSc: Systemic sclerosis
- TSS: Total skin score
- VDRL: Venereal disease research laboratory
- VLDL: Very low density lipoprotein
- WBCs: White blood cells
-WHO: World Health Organization

SYSTEMIC LUPUS ERYTHEMATOSUS

Introduction

Systemic lupus erythematosus (SLE) is a chronic multisystem autoimmune disease with a broad range of clinical manifestations, including photosensitive skin rashes, discoid lesions, arthritis/arthralgia, nephritis, cardiac and pulmonary disease, and CNS disorders. The disease pathogenesis is attributed to circulating antinuclear autoantibodies against a variety of nuclear antigens (including dsDNA, the ribonucleoprotein (RNP) complex Ro, the RNA-binding protein La, RNPs, the RNA molecule/protein complex Sm, the C1 complement component subunit C1q, and phospholipids) and the dysfunction of T and B lymphocytes and dendritic cells (**D'Cruz et al., 2007)**.

Clinical manifestations may be constitutional or result from inflammation in various organ systems, including skin and mucous membranes, joints, kidney, brain, serous membranes, lungs, heart and occasionally the gastrointestinal tract. Organ system may be involved simply or in any combination (**Gladman and Urowitz, 2008**).

The pathogenesis of systemic lupus erythematosus is complex (**Croker and Kimberly, 2005**). Target tissue damage is caused by pathogenic auto-antibodies and immune complexes. The abnormal immune responses that permit persistence of pathogenic B-cells and T-cells has multiple components including activation of innate immune response by DNA–containing and RNA–containing antigens (**Hahn et al., 2009**).

Although the pathogenesis is believed to lie in the dysregulation of the immune system, the involvement of various organ systems often leads to secondary morbidities resulting from renal failure, hypertension, or CNS disorders, and more recently it is becoming increasingly clear that accelerated atherosclerosis associated with SLE may contribute to premature mortality **(Petri, 2000).**

The heart is one of the major targets of Systemic lupus erythematosus. Cardiovascular manifestations involving the pericardium, myocardium, endocardium, and coronary vessels have been found **(Leszczynski et al., 2003).**

The most frequent cardiovascular complications in diffuse connective tissue diseases patients are hypertension, hyperlipidemia and coronary artery disease. The prognosis of patients complicated with cardiovascular diseases is poor. SLE patients are younger at onset of cardiovascular diseases **(Deng et al., 2010).**

Coronary artery disease in lupus is primarily a manifestation of generalized atherosclerosis (**Gladman and Urowitz, 2008**).

It is important to determine the presence of subclinical coronary artery disease in patients with autoimmune disease by noninvasive studies such as Sestamibi single photon emission tomography (SPECT) for assessment of myocardial perfusion in order to plan an adequate treatment and follow-up **(Espinola et al., 2005).**

Pulmonary hypertension (PH) is not a rare concomitant disease in SLE patients. The presence of Rayuand's phenomenon, fingertip vasculitis, anti-U1RNP antibody positivity, antiphospholipid antibody positivity, pericardial effusion, and interstitial pneumonia all suggest the likeliness of PH in SLE patients, and echocardiographic examination may help derive an early diagnosis **(Luo et al., 2008).**

Renal disease is a major cause of morbidity and hospital admission in SLE patients and occurs in 40% to 70% of all patients. Renal involvement tends to occur within the first 2 years of SLE with its frequency decreasing significantly after the first 5 years of disease. The disease displays a remarkable clinical and histological heterogenecity (**Tassiulas and Boumpas, 2009**).

Involvement of central and peripheral nervous systems in SLE is a major cause of morbidity and mortality. Nervous system involvement in SLE is the least understood manifestation of the disease and remains a complex diagnostic entity as a result of its multiple clinical presentations (**Tassiulas and Boumpas, 2009**).

Cardiopulmonary Involvement in Systemic Lupus Erythematosus

Heart involvement

1- Myocarditis

Myocarditis occurs in about 9% of patients with SLE. It may be accompanied by other cardiac manifestations or be an isolated cardiac feature. Myocarditis should be suspected in patients who present with arrhythmias or conduction defects, unexplained cardiomegaly with or without congestive heart failure or unexplained tachycardia. Congestive heart failure is a less common feature of SLE and is usually secondary to a combination of factors, which may include myocarditis (**Wijetunga and Rockson, 2002**).

Sasson et al., 1992 using pulsed Doppler echocardiography demonstrated left ventricular dysfunction in 64% of patients with active SLE and 14% of patients with inactive SLE all of whom did not have any clinical evidence of cardiac disease, had normal echocardiograms, and evidence of pericardial or valvular disease.

Cacciapuoti et al., 2005 calculated the myocardial performance index (MPI) in 44 patients with SLE without any cardiac complaints and normal cardiac structure. MPI was prolonged in SLE patients compared to healthy controls. In a study done by **Hosenpud et al 1984,** they found abnormal thallium scans in 10 of 26 patients with randomly selected SLE.

2-Endocarditis

Endocarditis is very difficult to discern in lupus, because the majority of murmurs heared clinically are not associated with any organic valvular disease or investigations (**Gladman and Urowitz, 2008**). Non-bacterial verrucous vegetations described by Libman & Sacks are found in 15% of patients at autopsy. Vegetations may vary from mere valvular thickening, detected by two-dimensional

echocardiography to very large lesions causing significant valvular dysfunction (**Straaton et al., 1988**).

3-Pericarditis

Pericarditis is the most common cardiac manifestation of SLE and is found in approximately one quarter of SLE patients. Pericardial effusions may be asymptomatic and are usually mild to moderate. Tamponade is rare, but can occur (**Tassuilas and Boumpas, 2009**).

Pulmonary manifestations of systemic lupus erythematosus

At some time during their course, most patients with systemic lupus erythematosus show signs of involvement of the lung, its vasculature, the pleura, and/or the diaphragm **(Kim et al., 2000).** Pulmonary involvement in SLE may consist of lupus pleuritis, lupus pneumonitis, pulmonary hemorrhage, embolism or pulmonary hypertension (**Boumpas et al., 1995**).

Pleurisy, coughing, and/or dyspnea are often the first clues to either lung involvement or SLE itself **(Hellman et al., 1995)**. In some cases, however, abnormal pulmonary function tests, including the diffusing capacity for carbon monoxide and/or abnormal chest x-rays may be detected in asymptomatic patients. Pulmonary abnormalities do not correlate with immune parameters **(Nakano et al., 2002)**.

Patients with SLE and lung involvement must always be evaluated for infection, particularly that due to bacteria and viruses. Given that many are immunocompromised, tuberculosis, fungal infections, and other opportunistic infections should also be considered **(Rojas et al., 2008).**