EVALUATION OF CORONARY ARTERY DISEASE IN SYSTEMIC LUPUS ERYTHEMATOSUS AND SCLERODERMA: CORRELATION WITH PULMONARY HYPERTENSION 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 scleroderma (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 scleroderma 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: Bronchialveolar 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: Prostacyclin
- PH: Pulmonary hypertension
- RA: Rheumatoid arthritis
- RNA: Ribonucleic acid
- RNP: Ribonucleoprotein
- Scl-70: Scleroderma-70
- SLE: Systemic lupus erythematous
- SLEDAI: Systemic lupus erythematous 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 (Leszcynski 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 heterogeneity (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).
Chest pain on breathing occurs in approximately 50 percent of patients with SLE. It may be due to musculoskeletal causes or pleurisy (Pope, 2008).

1-Musculoskeletal pain

The most common cause of chest pain in SLE is from muscles, connective tissues, or costochondral joints. The chest pain is characterized by painful deep breaths, aggravated by motion or change of position, and is elicited by palpation of the painful areas (Schur et al., 2009).

2-Pleurisy

Inflammation of the pleura may cause chest pain in the absence of a friction rub or radiographic evidence of a pleural effusion. In this setting, it is often difficult to determine whether the chest pain represents pleuritis. However, the presence of a rub, sometimes transient, and/or a pleural effusion facilitates the diagnosis. The effusion is usually small or moderate, although large effusions have been noted. They tend to be evanescent and recurrent and are often bilateral (Rothfield, 1983).

The pleural effusion in SLE is a mild exudate characterized by an elevation in pleural fluid LDH but not signs of marked inflammation. The findings differ from those in other conditions, particularly rheumatoid arthritis. The total white cell count (with a predominance of either lymphocytes or polymorphonuclear cells) is lower in lupus-related effusions. However, there is substantial overlap, so that the white count in an individual patient cannot be used to establish the diagnosis. Pleural fluid glucose concentrations in lupus effusions are slightly lower than serum blood levels; by comparison, pleural glucose levels in rheumatoid effusions are significantly reduced (Turner and Turner, 1982).
Although the presence of rheumatoid factor or anti-nuclear antibodies in pleural fluid suggests RA and SLE, respectively, these findings provide no additional diagnostic information beyond that obtained from the measurement of these autoantibodies in serum and, therefore, these tests need not be performed on pleural fluid samples. Additional causes of pleural effusions, such as infection, congestive heart failure, and uremia, must also be excluded (Small et al., 1982).

3-Upper respiratory tract infection

Cough is often the only manifestation of pulmonary involvement in SLE. Cough is most often due to an upper respiratory infection, usually viral. Infections are more frequent in lupus, particularly in patients who are treated with glucocorticoids or immunosuppressive agents (Ginzler et al., 1978).

4-Acute pneumonitis

Acute lupus pneumonitis is an uncommon (1 to 12 percent) manifestation of SLE. Acute lupus pneumonitis is characterized by fever, cough (sometimes with hemoptysis), pleurisy, dyspnea, pulmonary infiltrates on x-ray (diffuse acinar infiltrates especially in the lower lung fields), hypoxia, basilar rales, pleural effusion (in 50 percent), serum anti-DNA antibodies, and no apparent infection (Matthay et al., 1975).

Pathologic examination in lupus pneumonitis reveals acute alveolar wall injury, alveolar hemorrhage, alveolar edema, hyaline membrane formation, and immunoglobulin and complement deposition (Lawrence, 1987). Some authors doubt the existence of this syndrome unless one of the following can be demonstrated: interstitial fibrosis, vasculitis, hematoxylin bodies, interstitial pneumonitis, alveolitis, or pleuritis (Haupt et al., 1981).
The diagnosis of alveolitis may be facilitated by the detection of late inspiratory crackles, and the presence of abnormalities on CT scanning, 67 gallium scintigraphy, or bronchoalveolar lavage (BAL) (Witt et al., 1996).

5-Chronic pneumonitis

Chronic (fibrotic) lupus pneumonitis has been noted in up to nine percent of patients with SLE in some series (Weidemann and Matthy, 1992). Patients with longstanding SLE, and possibly those with anti-Ro antibodies are more likely to develop chronic pneumonitis (Hedgpeth and Boulware, 1988).

Patients with chronic pneumonitis frequently suffer from the insidious onset of chronic nonproductive cough, dyspnea, and recurrent pleuritic chest pain. Pulmonary function studies show a restrictive pattern with reductions in lung volumes, diffusion capacity for carbon monoxide (DLCO), and arterial blood oxygen tension (Pope, 2008).

The clinical and pathological findings in chronic lupus pneumonitis are quite similar to those in idiopathic pulmonary fibrosis. In most cases, the presence of lupus is suggested by the characteristic extrapulmonary and serological manifestations (Schur et al., 2009).

This syndrome should be differentiated from pulmonary edema, acute respiratory distress syndrome, bilateral pneumonia, interstitial fibrosis, infection, malignancy, and granulomatous disease. Although chest radiographs reveal changes of chronic pneumonitis, important diagnostic tools which aid in distinguishing among these possibilities are high resolution computed tomography (HRCT), bronchoalveolar lavage, 67-gallium scintigraphy, and, when there is still uncertainty about the diagnosis following these less invasive studies, lung biopsy should be done (Witt et al., 1996).
High resolution computed tomography may be extremely helpful in showing two different patterns which are similar to those seen in scleroderma lung disease, a ground-glass appearance is associated with predominant cellular infiltration which on lung biopsy is most consistent with non specific pneumonia. In comparison, a reticular pattern is associated with primarily fibrotic disease which on lung biopsy is most consistent with usual interstitial pneumonia (Wells et al., 1993).

Conflicting results have been published concerning the correlation among HRCT findings, pulmonary symptoms, and physiologic studies. One prospective study of 34 patients with SLE found abnormalities detected by HRCT, pulmonary function studies, or chest radiography in 70, 41, and 24 percent, respectively (Fenlon et al., 1996). No correlation existed among HRCT, pulmonary function studies, and pulmonary symptoms. In contrast, another prospective study of 48 patients found that abnormalities on HRCT were associated with symptom duration and pulmonary function abnormalities (Bankier et al., 1995).

Bronchoalveolar lavage (BAL) can also be useful to exclude infection, malignancy, and granulomatous disease. The presence of more than 10 percent neutrophils on BAL is suggestive of chronic lupus pneumonitis; however, this finding may also be observed in patients with scleroderma, rheumatoid pneumonitis, and idiopathic pulmonary fibrosis (Lawrence, 1987).

Lung biopsy may be required if the diagnosis is still in doubt despite the less invasive tests described above. The histopathologic findings of chronic lupus pneumonitis include alveolar septal thickening, interstitial fibrosis, lymphocytic infiltrates, alveolar septal immune deposits, and type II pneumocyte hyperplasia (Lawrence, 1987). The most common pathologic patterns include nonspecific interstitial pneumonia (cellular or fibrotic), usual interstitial pneumonina, and sometimes lymphocytic interstitial pneumonia (Tansey et al., 2004).
6-Pulmonary hemorrhage

Pulmonary hemorrhage, not necessarily with hemoptysis, is a rare complication in SLE (Badsha et al., 2004). As an example, one study found pulmonary hemorrhage in only 19 of 510 patients who were hospitalized over a ten year period. Although pulmonary hemorrhage may be the presenting manifestation of SLE, it is most commonly observed in those who are already known to have lupus. The underlying etiology of the alveolar damage and pulmonary hemorrhage in this setting is unknown (Zamora et al., 1997).

Affected patients appear acutely ill, and commonly complain of dyspnea, hemoptysis, and cough. The bleeding may be sufficient to induce anemia, and some patients have concurrent lupus nephritis. Chest radiography frequently shows bilateral alveolar infiltrates, results suggestive of pulmonary edema or infection. Pulmonary magnetic resonance imaging may suggest hemorrhage, since the paramagnetic effects of iron (in hemorrhagic blood) result in preferential T2 shortening. Bronchoalveolar lavage may yield persistently bloody fluid with hemosiderin-laden macrophages, which (when present) helps exclude infection (Hsu et al., 1992).

The differential diagnosis in patients with this presentation includes aspiration, infection, pulmonary emboli, and vasculitis. While a significantly elevated diffusing capacity for carbon monoxide may be strongly suggestive of pulmonary hemorrhage, the diagnosis can be established definitively only by lung biopsy. Two different histologic patterns have been described: Patterns of capillaritis with immune complex deposition and bland hemorrhage have both been reported. The latter appears to be more common, accounting for 72 percent of cases in a recent report versus 14 percent with capillaritis (Schwab et al., 1993).