CARDIO-PULMONARY PROFILE
IN
SYSTEMIC SCLEROSIS

DISSERTATION

Submitted in partial fulfillment of the requirement for the degree of

D.M. BRANCH IX – RHEUMATOLOGY

THE TAMILNADU DR. MGR. MEDICAL UNIVERSITY
CHENNAI

2007

ACKNOWLEDGEMENT

I sincerely thank The Dean, **Dr. T. P. Kalaniti, M.D.,** for having permitted me to carry out this dissertation work at Government General Hospital, Madras Medical College, Chennai.

I am highly indebted to **Prof. C. Panchapakesa Rajendran, M.D., D.M**., Professor and Head, Department of Rheumatology, Madras Medical College, Chennai, for his valuable suggestions, kind guidance, constant supervision and moral support without which this study would not have been possible.

I am highly thankful to **Dr. Sasikala Stephen, M.D.,** Additional Professor, Department of Rheumatology, Madras Medical College, Chennai, for her valuable guidance.

I am extremely thankful to Assistant Professors, Dr. S. Rukmangatharajan, M.D., D.M., Dr. P. Kanakarani, M.D., D.M., Dr. S. Rajeswari, M.D.,D.M., Dr. R. Ravichandran , M.D.,D.M., and Dr. N. Vasanthy, M.D., Department of Rheumatology, Madras Medical College, Chennai, for their valuable guidance and keen interest in this work.

I am extremely thankful to Prof. V. Jeganathan, M.D., D.M., Professor and Head, Department of Cardiology, Madras Medical College, Chennai, for permitting me to carry out the cardiological evaluation for this work at the Department of Cardiology, Madras Medical College, Chennai.

I am sincerely thankful to Prof. D. Ranganathan, D.T.C.D., D.N.B., Professor and Head, and Assistant Professors Dr. V. Sundhar M.D., D.T.C.D., and Dr. Vinothkumar M.D., D.T.C.D., D.N.B, Department of Thoracic Medicine, Madras

Medical College, Chennai, for their help in carrying out the broncho-alveolar lavage study and pulmonary function tests.

I am extremely thankful to Prof. T. S. Swaminathan, M.D., Director, Bernaud Institute of Radiology, Madras Medical College, Chennai, for his invaluable help to carry out HRCT studies for this study purpose.

I am very much thankful to the laboratory personnel Mr. R. Sajjad Ahamed, Mr. K. R. Hariharan, Mrs.C. Radhabai, and Mrs. Kumudha Manoharan, for their invaluable help and perseverance for carrying out the immunological investigations without which this work would not have been possible.

I am deeply indebted to my father, wife and children for their constant encouragement and moral support.

CERTIFICATE

This is to certify that the dissertation entitled “Carido-pulmonary profile in systemic sclerosis”, is a bonafide work of **Dr. T. N. Tamilselvam,** during the period from August 2004 to July 2007, in partial fulfillment of the requirement for the degree of D.M. Rheumatology (Branch IX) of The Tamilnadu Dr. M.G.R. Medical University

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CONTENTS

INTRODUCTION

Systemic sclerosis is a generalised disorder of connective tissue(1) characterized clinically by thickening and fibrosis of skin and by distinctive form of involvement of internal organs, notably the heart, lungs, kidneys and gastrointestinal tract(2). Morbidity and mortality are substantial and are directly related to the extent and severity of visceral involvement (1). Scleroderma or systemic sclerosis is characterized by fibrosis and micro vascular occlusion. These two processes are seen in all involved organs of patients with systemic sclerosis.

The etiology of systemic sclerosis remains elusive despite significant advances in the understanding of the pathogenic mechanisms of the disease since its initial description in the medical literature almost 250 years ago. Systemic sclerosis (SSc) can be conceptualized as tripartite disease in which dysfunction of the immune system, endothelium, and fibroblasts give rise to a heterogeneous phenotype that is marked by prominent fibrosis(3).

Autoimmunity is manifested by the elaboration of circulating disease specific auto antibodies (4). Fibroblast dysfunction is manifested as fibrosis of skin and internal organs as the result of increased synthesis and deposition of extra cellular matrix (ECM) proteins (5, 6). Raynaud's phenomenon, capillary dropout, endothelial injury/apoptosis, and abnormalities in vascular tone are manifestations of endothelial cell dysfunction.

Genetic factors may play a role in the dysregulation of these components by affecting host susceptibility to disease or modifying clinical presentation and organ

damage. Available data are consistent with the paradigm that the phenotype identified as SSc is the end result of a complex interaction of genetic factors and unknown environmental influences.

The pathologic hallmark of systemic sclerosis is an excessive accumulation of extra cellular matrix (ECM) in the dermis, which leads to taut skin. Thinning of papillary dermis with deposits of fibrinonectin, glycosaminoglycans and tenacin play a crucial role. In the early stages of systemic sclerosis, an infiltration of mononuclear inflammatory cells, predominantly T cells (8), surrounding the dermal blood vessels is concentrated at the border between the reticular dermis and subcutaneous fat. There is intimal proliferation with luminal narrowing at the arterial and arteriolar levels. Capillary loss can be seen in vivo in the skin by wide field nail fold capillaroscopy. (9).

One of the vascular hallmarks of systemic sclerosis, of either the limited (subcutaneous ***C***alcinosis, ***R***aynaud's phenomenon, ***E***sophageal dysmotility, ***S***clerodactyly, ***T***elengiectasia CREST syndrome) or diffuse form of the disease, is telengiectasia over the face, hands and anterior chest. Fibrotic and vascular lesions occur in the lungs of patients with systemic sclerosis. Marked intimal proliferation with narrowing of the lumen is accompanied by medial thickening resulting in pulmonary hypertension, and eventual right heart failure. The initial stage of the pulmonary fibrotic lesion is inflammation within the alveolar air spaces (10)

Scleroderma is a generic term used to describe both disease restricted to the skin(localized scleroderma) and disease with internal organ involvement.(systemic sclerosis).There are two main categories of systemic sclerosis, limited cutaneous

systemic sclerosis (lSSc) and diffuse systemic sclerosis(dSSc). Limited cutaneous systemic sclerosis is skin thickening confined to the extremities distal to the elboews and knees, without truncal involvement (facial involvement is permitted).Diffuse cutaneous systemic sclerosis is skin involvement that, at one time, includes the proximal extremities or the trunk.Scleroderma sine scleroderma describes about 5% of systemic sclerosis patients who have no skin involvement but do have characteristic gut or other internal organ damage.

Limited cutaneous systemic sclerosis is more common than the diffuse version of the disease, but exact ratios are unknown because of a bias towards under-diagnosis. Patients with the CREST syndrome of Calcinosis, Raynud's phenomenon, Esophageal dysmotility, Sclerodactyly, and Telengiectasia are a subset of limited cutaneous patients. Other patients with lSSc (limited cutaneous systemic sclerosis) or dSSc (diffuse cutaneous systemic sclerosis) may have calcinosis, Raynaud's phenomenon, esophageal dysmotility, or telengectasia and systemic sclerosis patients are not given the diagnosis of CREST just because they have one or more of these later manifestations.

Limited cutaneous patients with anticentromere antibodies are at lower risk of developing interstitial lung disease than other patients, but are at high risk of pulmonary hypertension. Limited cutaneous patients are at less risk of developing heart involvement, renal crisis, and pseudo- obstruction. Patients with dSSc usually present progressive skin thickening, fatigue, anorexia, and weight loss. This subset of patients is more likely to develop interstitial lung disease and pulmonary hypertension.

HEART:

Pericardial and myocardial lesions can occur in systemic sclerosis. Fibrosis and occasional constriction can occur at pericardium. The myocardium shows intimal proliferation and luminal narrowing of the small vessels. Surrounding the damaged blood vessels is fibrosis replacing the myocardium. The early lesion is contraction band necrosis. The histologic evidence suggests the primary insult in the myocardium is ischemic and is the result of structural vascular disease and vasospasm. (11). Gastrointestinal tract, kidneys, musculoskeletal system can get involved in the pathogenetic process showing variable involvement (12)

Evidence from multiple sources indicates that SSc does not occur randomly at population. Incidence at United States is 20 per million per year. The incidence tends to remain stable in some areas whereas incidence and prevalence seems to vary in different areas. Survival has improved over past few decades. Mean survival is 12 years from diagnosis (13). Renal disease accounts for early mortality, but pulmonary disease has emerged as a major cause of death and is associated with a poorer prognosis. Women are affected more frequently than men but the exact cause of this is not known. Some studies predict that the number of pregnancies may influence later disease expression (14).

Racial factors play a role in disease susceptibility and expression. Age specific incidence rates are higher in black women than in white; the greatest difference occurs in the young to middle adult age group (15) (less than 54 years of age).

Diffuse occur more commonly in blacks than in whites. Age at onset of diffuse is younger than the onset of limited disease. It is likely that there is a strong interplay among genetic factors, hormonal or reproductive-related events, and an external trigger that must interact to result in clinical disease.

Heine in 1926 and Weiss and colleagues in 1943 were the first to report cardiac involvement in SSc. Clinical presentation of cardiac involvement include dyspnea, features of pulmonary hypertension, palpitation, CCF, aypical chest pain, typical angina occasionally, and cardiomyopthy. Cardiac involvement is often clinically occult and the prevalence of cardiac disease varies depending on the methods used to define the cardiac involvement. Myocardial fibrosis is the hallmark of cardiac involvement. SSc cardiac fibrosis may involve the immediate subendocardial layer, typically spared in atherosclerosis. Systolic and diastolic dysfunction may occur. Conduction disturbances and pericardial involvement may occur. Cardiac involvement in limited and diffuse disease vary.

INTERSTITIAL LUNG DISEASE IN SYSTEMIC SCLEROSIS

Lung involvement in systemic sclerosis is almost universal and now accounts for significant morbidity. Both interstitial fibrosis and pulmonary arterial vascular disease are present in the lungs of patients with scleroderma but often one pathologic process will be the dominant cause of clinical problems. Pulmonary interstitial fibrosis is more likely to be severe in patients with diffuse disease while pulmonary vascular disease and pulmonary hypertension can be the dominant problem of the lung in patients with CREST syndrome.

Most patients have some degree of both processes and all patients with interstitial lung disease and pulmonary hypertension should be evaluated thoroughly. 80% of patients will have abnormal PFT (Pulmonary Function Tests) measured by specific and sensitive testing. Yet, the majority of the lung disease will be clinically silent until advanced pulmonary fibrosis or moderate to severe pulmonary arterial hypertension is present. Dyspnea on exertion is the initial complaint and dry cough a late feature of ILD (Interstitial lung disease). Velcro-like crackles at lung bases are characteristic. Chest radiograph is relatively insensitive but if abnormal, the fibrosis appears as bilateral reticulonodular changes in the lower lobes of the lung parenchyma.

PFT shows a restrictive type of ventilatory defect. The most common abnormality is reduced diffusion capacity or a reduction in lung volumes (forced vital capacity) typical of a restrictive defect with associated reduction in gas exchange. HRCT (High resolution computed tomography) is very sensitive for detecting changes in lung parenchyma. Findings of ground glass opacification of the lung bases on HRCT correspond with active alveolitis and progressive restrictive lung disease. Bronchoalveolar lavage(BAL) is used to detect inflammation and active alveolitis. BAL demonstrates an increased total number of cells with an increase in neutrophils, eosinophils or CD8+ T cells. Evidence of active alveolitis by either BAL or HRCT predicts progressive lung disease.

Pulmonary arterial vascular disease with associated pulmonary hypertension is one of the difficult clinical situations in systemic sclerosis. The pulmonary vascular process can be indolent and remain clinically undetectable until severe irreversible

pulmonary hypertension and right sided cardiac failure develop. The natural course of the lung disease is variable. The majority will have an early but modest decline in function and then follow a stable course or improve. One third will have a more severe progressive decline in lung function that continues for 4-5 years and then stabilize.

REVIEW OF LITERATURE

Like other connective tissue disorders, systemic sclerosis is also predominant in females, 3-5:1 most commonly, but as high as 14:1 in some populations. The female: male ratio is greatest in childbearing years.

Steen VD et al described age of onset of scleroderma is most commonly in the range of 30-50 years. (38). The mean age of onset in white men and women are 44 and 42 years. This is similar in patients in both subsets of scleroderma, limited cutaneous and diffuse cutaneous, although patients with limited scleroderma not usually diagnosed until 5-10 years later.

Walker UA et al in their study of clinical risk assessment for organ manifestations in systemic sclerosis and in order to better understand the vascular, immunological and fibrotic processes of SSc and to guide its treatment studied a total of 3656 patients (1349 with dcSSc and 2101 with lcSSc), enrolled in 102 centers and 30 countries and concluded that 1330 individuals had auto antibodies against Scl70 and 1106 against anticentromere antibodies and 87% of patients were female. On multivariate analysis, scleroderma subsets (dcSSc vs lcSSc), antibody status and age at onset of Raynaud's phenomenon, but not gender were independently associated with the prevalence of organ manifestations.

The **Eustar Meds** data base facilitates the analysis of clinical patterns in SSc and contributes to the standardized assessment and monitoring of SSc internationally (17).

Sharma et al in their study have reported the clinical and immunological profile of patients from North India between 2001 and 2004 .84 females and 16 males with systemic sclerosis with mean age of 32 were reported. The reported profile included Raynaud's phenomenon in 92.9%, ANA positivity in 89.1%, abnormal chest X ray in 65.3% and reduced pulmonary function test in 85.8% and these features in North Indian population was similar to that of other ethnic groups (18).

Krishnamurthy et al have reported a study of 78 patients and they have reported a female preponderance(3.5:1) with a peak age of occurrence in the 4^{th} decade(32%), Raynaud's phenomenon in 28%,ANA positivity in 56.8%,abnormal echocardiography in31% and restrictive type of pulmonary function in 55%(19).

SCLERODERMA CLASSIFICATION AND SUBSETS:

The epidemiology and natural history of scleroderma revolve around the two major scleroderma subsets. The American College of Rheumatology criteria for the classification (not diagnosis) of scleroderma was established in 1980. The major criterion is skin thickening proximal to the metacarpophalangeal joints; minor criteria (two of the minor criteria are required) include sclerodactyly, digital pitting scars or loss of digital finger pad substance and bibasilar pulmonary fibrosis. Patients had to have had symptoms for less than 2 years. This resulted in a smaller number of patients with limited scleroderma, because the early diagnosis of limited scleroderma is infrequent.

Patients with limited diseases have skin thickening of distal extremities and face. They may not have all the features of CREST syndrome, although many of them

do. The extent of the skin thickening and the pace of the disease differentiate limited and diffuse skin disease. The disease onset in patients with limited scleroderma is usually with Raynaud's phenomenon, which is alone present for years before any other manifestations occur; at some time, possibly 5 -10 years later, they develop puffy, swollen fingers, digital tip ulcers, telengiectasis or esophageal symptoms enabling a diagnosis of limited scleroderma. In contrast, patients with diffuse cutaneous disease have a much more acute onset of symptoms including Raynaud's phenomenon, swollen hands and legs, carpal tunnel syndrome, arthralgia /arthritis and fatigue, all occurring in a short span of time.

Diagnosis of diffuse scleroderma occurs usually after skin thickening becomes evident, 1 -12 months after the onset of other symptoms. The pattern of organ involvement is also different. Interstitial fibrosis occurs in both forms and is related to the anti Scl-70 antibody. Isolated pulmonary hypertension occurs more prominently in limited scleroderma, whereas renal disease and cardiac disease occur predominantly in diffuse scleroderma.

Classically, the anticentromere (ACA) antibody is seen in limited scleroderma with greater frequency in women. It is seen in 30 to90% patients with limited scleroderma (20). Antitopoisomerase-I or Scl-70 is the other scleroderma antibody for which commercial tests are available. However, about 25% of these patients do not have extensive skin, heart or kidney problems and their disease follows a course similar to that of limited scleroderma. In addition with the association with diffuse cutaneous disease, Scl-70 is associated with more pulmonary interstitial fibrosis and more vascular problems.

However these patients are protected from the isolated vasculopathy type of pulmonary hypertension. Cardiac disease and renal crisis complicate clinical picture when Scl-70 is present. Anti-RNA polymerase III is another commonly seen scleroderma specific antibody, which is found almost exclusively in diffuse scleroderma (28%), but assays are commercially not yet available.

A nucleolar pattern of antinuclear antibodies is very specific to scleroderma, and three different specific antibodies have been identified. One of them, anti U3 RNP or antifibrillarin, is the most frequent antibody seen in African Americans. It is associated with diffuse disease, pulmonary fibrosis, and isolated pulmonary hypertension. The other nucleolar antibodies, anti Th/To and anti Pm/Scl, are more frequent in patients with limited scleroderma. Pulmonary hypertension and myositis are common in patients with these antibodies. The most recently described scleroderma specific autoantibody is an auto antibody to fibrillin-1, a major structural protein of connective tissue micro fibrils(21).

The etiology of these auto antibodies is not very clear. They have not been shown to be pathogenic, but clearly appear to be markers of specific forms of the disease. They are almost seen at the time of physician evaluation and rarely disappear. They could be present for years before the onset of symptoms. One possibility is that they represent body's reaction to different triggers of the disease, perhaps environmental or occupational. In general, countries that have a large number of patients with limited scleroderma have a high frequency of anticentromere antibody. This strongly suggests that the anti-bodies are directly related to the subset of patients, and thus may play a larger part in the pathogenesis than do other factors.

Genetic factors:

Genetic factors appear to have a pathogenic role in scleroderma. Chromosomal breakage have been implicated but not conclusively proven. More recent data have been based on variable number tandem repeats, a technique that can show chromosomal abnormalities (22). Other pathogenic theory is that of microchimerism, in which the hypothesis is that the patients have a reaction to fetal cells from an early pregnancy or from their parents (in order to account for the occurrence in males and nulliparous females) (23) after which the patients develop a graft versus host reaction that results in scleroderma. Although the supporting data are reasonable, no correlation between scleroderma subtypes and auto antibodies is noted. But this is not fully tenable due to primary differences between graft Vs host disease and scleroderma.

Major histocompatability complex alleles did not have a major association with systemic sclerosis. A 1987 study showed that C4A-null alleles had the greatest association. DQA2, B8, DR3, and DQ2 have all been implicated. Some authors opine that DQ7 and DQ5 are more common (24). Limited types are correlated with HLA DR1 and diffuse types with DR5. Having a first degree relative with systemic sclerosis is the strongest risk factor for the disease

OCCUPATIONAL AND ENVIRONMENTAL RISK FACTORS:

Silica exposure, vibration, polyvinyl chloride and variety of other organic solvents tend to produce a scleroderma like illness. Drugs have been implicated with the development of scleoderma including appetite suppressants, 1-5

hydroxytryptophan, bleomycin, pentazocine and cocaine. Despite strong suspicion it has not been able to implicate silicon breast implants with systemic sclerosis.

CARDIAC INVOLVEMENT IN SYSTEMIC SCLEROSIS

In the study of **Walker UA et al**, palpitations, dyspnea on exertion, and chest discomfort are described as common features(17).They have reported palpitations in 34%,dyspnea in 47% and chest discomfort in 31% of their patents. **Follansbee et al** study revealed pericarditis, congestive cardiac failure, pulmonary hypertension and arrhythmias are the main categories of cardiac disease seen in both subtypes of systemic sclerosis (25). Dyspnea on exertion is more often due to scleroderma lung disease than due to cardiac involvement until late in the course of the disease.

Follansbee et al noted clinical evidence of cardiac disease in 20 to 25% of patients with systemic sclerosis(26). Palpitation, atypical chest pain, or syncope may be due to arrhythmias or pericardial disease. Ischemic chest pain and myocardial infarct are uncommon.

Steen VD et al noted that the thallium perfusion defects reflecting vascular disease of endomyocardial vessels (not larger coronary vessels) are seen both at rest and during exertion. Cold provocation of Raynaud's phenomenon can temporarily increase the nature of thallium perfusion defects and induces abnormalities of ventricular wall motion indicating that reversible vasospasm of the myocardial circulation occurs in scleroderma. Patchy myocardial fibrosis can occur due to ischemic reperfusion events in the heart musculature causing contraction band

necrosis of cardiac muscle. Left and right ventricular dysfunction is common in scleroderma and diastolic dysfunction can occur independent of systolic dysfunction.

Steen and Follansbee et al suggested abnormal left ventricular compliance and pulmonary vascular congestion may occur either due to fibrosis of cardiac muscle or due to hypertension(27). Myocarditis may be associated with inflammatory muscle disease and may be associated with congestive cardiac failure (CCF) or sudden cardiac death. Myocarditis in systemic sclerosis has to be differentiated from muscle fibrosis in systemic sclerosis.

In a study of 100 patients with SSc, **Akesson and Wolheim** noted that cardiomegaly was present in 24% of patients with diffuse scleroderma and in 3 % of those with CREST syndrome and an abnormal ECG was present in 35% of the diffuse and 25% of limited type (28).

Follansbee et al compared results of radionuclide evaluation of 22 patients with limited scleroderma and 26 patients with diffuse scleroderma. Thallium perfusion defects were present in 64% of the limited patients whereas 77% of diffuse had defects. In contrast to the diffuse scleroderma patients, thallium perfusion defects in the limited scleroderma patients appeared to be functionally not significant. A reduced ejection fraction was noted in 36%of patients with limited type. This was due to secondary pulmonary hypertension resulting from pulmonary vascular disease in patients with limited scleroderma which is rare in diffuse scleroderma (29)

Kinney E et al reported that mild valvular abnormalities in the form of thickening of the mitral valve, mitral valve prolapse and verrucous endocarditis may

also be seen in patients with the CREST syndrome(30). Electrocardiographic abnormalities and arrhythmias have been reported in both limited and diffuse cutaneous types.

Geirsson et al noted that resting ECG abnormalities were present in 38% with limited and 38% of patients with diffuse SSc(31). Using univariate analysis, **Kostis et al** observed that supraventricular and ventricular tachycardia were more frequently found in patients with diffuse scleroderma. The extent of skin involvement, however, was not a predictor of arrhythmias or mortality in multivariate analysis (32).

Conduction system disease and arrhythmias may be revealed by ECG and Holter monitoring. Premature ventricular contractions are most common arrhythmias. Premature atrial contractions, supraventricular tachycardias, atrioventricular or intraventricular conduction disturbances are seen less commonly. Arrhythmias are quite common in diffuse type.

PRIMARY PULMONARY HYPERTENSION IN SYSTEMIC SCLEROSIS

Christopher et al documented a prevalence of 12to 15% of primary pulmonary hypertension in a hospital based cohort study. In a retrospective study, **KOH et al** reported 4.9% of pulmonary hypertension. In this study 8 patients had primary pulmonary hypertension and 9 patients had secondary pulmonary hypertension. Patients with interstitial lung disease developed pulmonary hypertension earlier, but had longer survival than patients with primary pulmonary hypertension

Stupi AM et al observed pulmonary hypertension in 9% of patients with systemic sclerosis. In 20 of 673 patients primary pulmonary hypertension was demonstrated. **Chang B et al** reported mild to moderate pulmonary hypertension in 26% of 361 patients and 13.6% of severe pulmonary hypertension. In this study patients with mild to moderate pulmonary hypertension had a 17% probability of progressing to severe PHT and 15% probability of regressing to no PHT.

De Azevedo et al documented 28% of PHT in 57 patients of which 8 patients had primary pulmonary hypertension and 8 patients had secondary pulmonary hypertension.

PULMONARY HYPERTENSION AND INTERSTITIAL LUNG DISEASE:

The two major pulmonary problems occurring among SSc patients are pulmonary hypertension and interstitial fibrosis. Isolated pulmonary hypertension occurs primarily in patients with limited cutaneous SSc in the absence of significant pulmonary fibrosis, whereas interstitial fibrosis occurs in either limited or diffuse cutaneous SSc.

PULMONARY VASCULAR DISEASE:

Pulmonary hypertension may occur as a primary process or secondary to interstitial lung disease and is found in 35% to 80% of systemic sclerosis depending upon the study population and the method of detection. Clinically detectable severe pulmonary hypertension is noted to occur in 9% of systemic sclerosis patients. Pulmonary hypertension is defined as resting pulmonary artery pressure greater than

25mm of Hg or an exercise pulmonary artery pressure (PAP) greater than 30mm of Hg.

Most common physiologic abnormality is a reduced diffusing capacity for carbon monoxide (DLCO). An isolated decrease in DLCO (<55%) is associated with the development of pulmonary hypertension (PHT) in patients with SSc of limited type. Pulmonary vasospasm may be important for the pathogenesis of a diminished DLCO and pulmonary hypertension in SSc.

Raynaud's phenomenon occurs in 90% of SSc patients and virtually in all the patients with limited type and pulmonary hypertension. Secondary causes of pulmonary hypertension include SSc heart disease and interstitial fibrosis.

Pulmonary hypertension due to parenchymal lung fibrosis may occur in patients with either limited or diffuse cutaneous SSc. Interstitial lung disease causes compression and obliteration of small pulmonary vessels, resulting in a decrease of pulmonary blood volume and vital capacity (VC). The diminished VC and decreased pulmonary volume result in an increased pulmonary vasculature resistance and in pulmonary hypertension.

The most common symptom of pulmonary hypertension is dyspnea and one third may be asymptomatic. Physical examination might reveal a raise in jugular venous pressure, a pulmonary lift, loud pulmonary component of S2 and a right ventricular gallop. The anticentromere antibody is specific for limited cutaneous SSc with greater than 95% anticentromere antibody (ACA) positive patients having limited cutaneous systemic sclerosis. Only 43% of patients with limited cutaneous

SSc, however, are ACA positive. Presence of ACA in limited cutaneous systemic sclerosis is associated with a decreased likelihood of interstitial lung disease but does not predict the likelihood of pulmonary hypertension.

Sullivan et al in a study demonstrated 73% patients with pulmonary hypertension had an abnormal chest radiograph or pulmonary function tests. Echocardiogram may show right ventricular enlargement, asymmetric septal hypertrophy, paradoxical septal motion or signs of pulmonary hypertension. Echocardiography is the most effective non invasive method for detecting moderate to severe pulmonary hypertension.

INTERSTITIAL LUNG DISEASE:

The prevalence of pulmonary fibrosis in scleroderma varies from 25% to 90% depending upon the method used to identify ILD. The restrictive lung disease on pulmonary function tests (PFT) is used as the defining abnormality.

The major clinical feature of SSc interstitial lung disease is a restrictive ventilatory defect causing dyspnea on exertion and non productive cough with bilateral crackles on auscultation. Pulmonary function tests (PFT) reveal a reduced forced vital capacity (FVC) and forced expiratory volume in one second (FEV1); residual volume and total lung capacity are reduced. Chest X ray may show linear and reticular shadows and in more advanced cases a honey comb appearance. Chest radiography is not as sensitive as high resolution computed tomography (HRCT) (33) Patchy areas with ground glass appearance correlate with acute cellular histopathology, whereas reticular shadows correspond to areas of fibrosis. In chronic

diffuse infiltrative lung disease, pathologic correlation indicates that areas with ground glass attenuation not associated with traction bronchiectasis or bronchiolectasis are reliable indicators of inflammation. Ground glass opacification correspond to neutrophilic alveolitis by broncho alveolar lavage (BAL) analysis.

Steen VD et al noted 23% of 88 American patients with limited type 40% of 77 patients who had diffuse disease had pulmonary fibrosis.

Owens GR et al predicted pulmonary fibrosis base on chest X ray in 33% patients with limited scleroderma and 40% of diffuse type patients(34).

Steen et al studied 165 nonsmoking patients by PFT and found that restrictive lung disease was the most frequent PFT abnormality(35)

Owens et al reported that 72% of CREST syndrome patients had abnormal pulmonary function. (36).

Harrison et al noted that the earliest to be lymphocytic and plasma cell infiltration of alveolar walls, interstitial fibrosis, increased macrophages in the alveolar spaces. Inflammatory alveolitis is an initial component of ILD. BAL studies have shown neutrophilic alveolitis in 50 to 60% of SSc patients. Increased number of eosinophils may also be present in the BAL fluid. The presence of neutrophilic alveolitis is associated with worse dyspnea and worse PFT’s and indicate a poor prognosis if untreated. BAL fluid analysis reveals lymphocytic predominance in early ILD.

The evolution of ILD involve differentiation of resident fibroblasts to a phenotype with increased proliferation and biosynthetic capacities is likely the result of the action of a variety of cytokines such as IL1, TNF alpha, IL6, IL8, and monocytic chemotactic protein (MCP). Chemotactic factors and chemokines produced by alveolar macrophages contribute and lead to perpetuation of fibrosis. Platelet Derived Growth Factor (PDGF) and transforming growth factor beta (TGF B) are two other essential cytokines in the evolution of interstitial lung disease (ILD).

PULMONARY HYPERTENSION IN SYSTEMIC SCLEROSIS

Colgan GT et al noted that pulmonary hypertension is present in 10 to 15% of SSc patients (48). Three aspects of PHT need emphasis. Pulmonary hypertension complicating limited cutaneous systemic sclerosis is a significant entity. Pulmonary hypertension arising from interstitial pulmonary fibrosis and lastly slowly progressive PHT in the course of limited cutaneous disease with secondary vascular component with mild fibrosis that is distinct fro severe interstitial fibrosis with secondary PHT.

PATHOGENESIS

The etiology of pulmonary hypertension in scleroderma spectrum disorders remains obscure. There appears to be a direct involvement of pulmonary circulation with intimal proliferation and medial hypertrophy similar to that seen in primary pulmonary hypertension. Some cases may also be related to severe pulmonary parenchymal disease, such as interstitial disease with hypoxemia.

Additionally diastolic dysfunctions of right and left ventricles have been seen in patients with scleroderma and may contribute to pulmonary hypertension.

Autoimmune processes have been implicated in the pathogenesis of pulmonary hypertension although the mechanism is not known. Positive antinuclear antibodies are frequently found in pulmonary hypertension patients without a diagnosis of connective tissue disease and pulmonary hypertension can occur before the onset of an identifiable connective tissue disease.

RAYNAUD'S PHENOMENON AND PULMONARY HYPERTENSION

Raynaud's phenomenon, vasospasm of arterioles in distal systemic circulation, is commonly reported in scleroderma. In one report all patients with PHT and CREST syndrome had Raynaud's while 68% without pulmonary hypertension had Raynaud's. Acute hypoxemic pulmonary vasoconstriction may be more pronounced in patients with PHT and SSc than in patients with primary PHT. Another report found that pulmonary vasospasm was not present in patients with Raynaud's and SSc without PHT.

The etiopathogenesis of PHT is complex and multifactorial. Major pathologic and histologic similarities exist between Primary pulmonary hypertension (PPHT) and systemic sclerosis associated PHT. In systemic sclerosis altered expression of TGF-B super family of receptors, interacting proteins or down stream signaling molecules occur in SSc. Some studies suggest single nucleotide polymorphisms with SSc . Wide spread endothelial cell activation occur in SSc as an earliest lesion. End stage lesion of PHT is microvascular luminal obliteration and alteration with medial and adventitial fibrosis and proliferative lesions and intimal hyperplasia. Plexiform lesions occur more commonly in primary pulmonary hypertension.

Elevated levels of ET-1 are a feature of PHT associated with systemic sclerosis (36). Deficiency in endothelium derived nitric oxide, excessive vasoconstrictors like endothelin-1, might contribute to pathogenesis. Less involved vessels may be vasodilated. The endothelin receptor blockade is antifibrotic and iloprost seems to down regulate expression of a potentially important, downstream proliferative mediator, the connective Tissue Growth Factor (CTGF).

The earliest symptom could be exertional breathlessness. Chest pain may occur due to right ventricular angina and syncope or near syncope due to reduced cardiac reserve. Emphasis should be on early diagnosis. PFT's, Doppler echocardiography and ECG aid in the definite diagnosis. Common PFT abnormality is reduction in carbon monoxide transfer factor with preservation of lung volumes. Isolated and often transient changes in CO diffusing capacity are common in SSc. This probably is due to ventilation perfusion alteration resulting in V/Q mismatch.

Echocardiography plays a vital role in Pulmonary arterial hypertension assessment .Structural changes that suggest elevated pulmonary artery pressure include increased pulmonary acceleration time, altered movement of inter ventricular septum, and impaired right ventricular function of pulmonary outflow dilatation. Peak systolic pressure can be assessed by the combination of echocardiography with Doppler assignment of regurgitant blood jet velocity through the tricuspid valve. Accuracy of the measurement is operator dependent and mild degree of regurgitation is hard to assess. With expertise Doppler echocardiography is highly specific and sensitive for detecting pulmonary hypertension. Strong correlation exists between

Doppler estimated peak pulmonary artery pressure and that measured by right heart catheterization.

The prevalence of PAHT is 5 to50% in various published series. The relationship between severity and pattern of SSc and pulmonary arterial bypertension (PAHT) is unclear. The isolated form is seen in classical limited cutaneous SSc and with anticentromere antibody reactivity. It is seen in diffuse cutaneous SSc and is associated with antifibrillarin (U3RNP) antibodies.

Monitoring of all patients with SSc and pulmonary hypertension at least by annual doppler echocardiogram and pulmonary function testing is not universally accepted as a standard practice. It is essential to have serial measurements of severity of pulmonary hypertension. This is accomplished with serial Doppler echocardiography, every 5 to 6 months depending upon clinical change, symptom severity and exercise capacity.

The 6 minute walk test has been established as a reproducible simple clinical measure of exercise capacity in pulmonary arterial hypertension which often used as an end point in clinical trails. It is to be performed regularly in all patients using a marked 50 meter course. There are defined levels of encouragement. Patients decide when the test is complete unless they exceed 500 meters.

OBJECTIVES

The objectives of the study are:

1. To study the cardiac manifestations in limited and diffuse cutaneous types of systemic sclerosis

2. To study the pulmonary manifestations including pulmonary hypertension in limited and diffuse cutaneous types of systemic sclerosis.

MATERIAL AND METHODS

This study was conducted in the department of Rheumatology, Madras Medical College and Govt. General Hospital Chennai during the period between August 2004 and December 2006.All the 63 consecutive patients with systemic sclerosis attending the Department of rheumatology, Govt. General Hospital, Chennai were included in this study. The patients fulfilling the American College of Rheumatology preliminary criteria for the classification of systemic sclerosis were included.

INCLUSION CRITERIA:

I. Major criteria:

Sclerodermatous skin change in any location proximal to the metacarpophalangeal joints

II. Minor Criteria:

1. Sclerodactaly

2. Digital pitting scars on finger tips or loss of digital finger pad substance

3. Bibasilar pulmonary fibrosis

Patients having the major and at least two or more of the minor criteria were included in this study.

The selected cases must be of 16 and above years of age

EXCLUSION CRITERIA:

1. Patients with overlap syndromes were excluded from the study

2. Patients with features of MCTD and UCTD were excluded.

3. Patients with previous history of tuberculosis and occupational lung disease were excluded

STUDY DESIGN

This study was an uncontrolled, prospective study conducted between August 2004 and December 2006. 63 patients satisfying the inclusion criteria were selected. Each patient underwent detailed historical assessment with thorough clinical examination. Systemic examination included detailed cardiovascular and pulmonary assessment clinically. The extent and severity of skin tightening was recorded with modified Rodnan skin scoring system. History, complaints, findings on physical examination was recorded in an investigator administered proforma. The proforma was as follows.

PROFORMA

Case No:

Name: Age: Sex:

I. PRESENTING COMPLAINTS

1. SKIN TIGHTENING

a. Diffuse cutaneous Yes / No

b. Limited cutaneous Yes / No

2. Raynaud's phenomenon Yes / No

3. Cardiovascular Features

a. Dyspnea Yes/ No

b. Palpitation Yes/ No

c. Chest pain Yes/ No

d. Syncope Yes/ No

4. Respiratory System

a. Cough Yes/ No

b. Hemoptysis Yes/ No

c. Chest pain Yes/ No

d. Dyspnea on exertion Yes/ No

PHYSICAL EXAMINATION

CVS

S1

S2 P2 loud / not loud

Added sounds

RS

NVBS

Pneumothorax

Velcro crackles

Features of fibrosis / Atelectasis / Consolidation / Collapse

INVESTIGATIONS

ECG

Echocardiography

Left atrial enlargement

Right atrial enlargement

Pericardial effusion

Left ventricular ejection fraction EF%

Fractional shortening (FS%) of RV

Tricuspid regurgitation / TRPG

Transmitral flow velocity

Transtricuspid flow velocity

Deceleration time

Pulmonary artery pressure (PAP)

Doppler tissue imaging (mitral annulus / tricuspid annulus)

X-RAY CHEST

HRCT of Chest

Pulmonary function tests (Spirometry)

Broncho alveolar lavage study

AUTO ANTIBODIES

Rheumatoid factor

Anti nuclear antibody

Scl – 70 anti body

LIMITATIONS OF THE STUDY

1. Diffusing capacity for carbon monoxide could not be tested as there is no availability

2. Anticentromere antibody profile could not be done.

3. 24 hrs continuous ambulatory ECG monitoring could not be accomplished.

All the eligible patients were subjected for the following investigations:

X Ray Chest PA view

Electrocardiogram

Echocardiogram with Doppler study

Pulmonary Function Tests (Spirometry)

Broncho alveolar lavage study (BAL)

High Resolution Computed Tomography

Laboratory Tests:

Rheumatoid Factor by Latex agglutination method

Antinuclear Antibody (ANA) by Indirect Immunofluorescence

Scl70 antibody by Elisa method

X ray Chest:

Chest X ray standard posteroanterior view was taken and was analyzed for features of cardiomegaly (CTR), pulmonary hypertension (Prominent pulmonary vasculature and pulmonary main artery (MPA), congestive cardiac Failure (CCF)-Kerley B Lines and pericardial effusion.

Lung fields were divided into 6 radiographic zones and assessment was done for the presence of interstitial lung disease (ground glass appearance, reticulonodular pattern, pulmonary fibrosis,), bronchiectatic changes, cystic lesions, pleural effusion, and pneumothorax.

ELECTROCARDIOGRAM:

12 lead standard resting electrocardiogram was recorded in all 63 patients. The ECG was analyzed for the following features:

Right and left atrial enlargement

Ventricular hypertrophy

Arrhythmias

Pericardial effusion

Ischemic changes, Non specific abnormalities of T wave and ST segment

ECHOCARDIOGRAPHY

Echocardiography was done for all the 63 patients by cardiologist. Pulmonary arterial pressure was determined. Doppler recordings were made from the parasternal, apical, and subcostal positions using modified views when appropriate. A systematic search was performed using two dimensional and color flow Doppler to identify the most regurgitant jet followed by continuous wave Doppler acquisition of spectral events of greatest maximal velocity and density. A control of 40 patients were included and the various measurements were recorded.

TWO DIMENSIONAL ECHOCARDIOGRAPHY

Pulmonary hypertension was recognized when the following M mode and 2D Echocardiographic features were present

Diminished or absent “a” (atrial) wave of pulmonary valve

Midsystolic closure or notching of the pulmonary valve

Enlarged chambers on the right side of the heart

D- Shaped left ventricular cavity caused by a flattened ventricular septum

Pulmonary hypertension is defined as a pulmonary artery systolic pressure (PASP) of 25 mm of Hg or more Pulmonary artery pressure control group: For the normal population, limited data are available on pulmonary artery pressure estimated by Doppler echocardiography. A study of 20 normal healthy adults by Vachiery et al using Doppler echocardiography found that the maximum estimated pulmonary artery pressure was 24 mm Hg.To assess the diagnostic validity of the results of the echocardiogram, a control group of 40 persons were subjected for echocardiogram and readings were incorporated into study.

DEFINITIONS

Pulmonary hypertension

The gold standard for pulmonary artery pressure measurement is invasive right heart catheterization. Pulmonary hypertension, defined by right heart catheterization of the pulmonary artery is a pressure of 25 mm Hg or greater at rest and at least 30 mm Hg during exercise Echocardiography has now widely used in patients with

cardiac disease. Correlations between Doppler and catheter measurements range from 0.89 to 0.91. The average standard error for systolic pulmonary artery pressure ranges from 5 to 9 mm of Hg and inter observer variability is <3%.

Pulmonary Function Tests:

Of the total 63 patients 53 patients underwent lung function testing within 1 week of echocardiographic examination. Pulmonary function testing was performed as per the, recommendations of American Thoracic Society. Values are interpreted as a percentage of predicted value.

Significant lung disease:

Significant lung disease that could be causing pulmonary hypertension was defined as pulmonary function measurements outside the normal range: a forced expiratory volume in 1 sec/forced vital capacity (FEV1/FVC) ratio of less than 65% or a vital lung volume of less than 80% of the predicted value. When PFT was abnormal patients were advised to undergo HRCT of lungs to see whether they have radiographic evidence of ILD. High resolution CT was performed in all the 63 Patients (Philips Tomoscan LX:Philips: Eindhoven, the Netherlands).Scans were performed at full inspiration in the supine position with 120 KV and 175 mA, including continuous scans through the lungs with 10 mm thickness followed by scans with 1.5-mm thickness with a slice spacing of 30 mm.

The patients were identified weather they had ILD or not. If they had features of ILD with HRCT with features of pulmonary hypertension they were identified to have secondary pulmonary hypertension. Occurrence of pulmonary hypertension

without associated ILD was known to be due to isolated primary type of pulmonary hypertension.

Broncho Alveolar Lavage

Fibroptic bronchoscope is wedged in to sub segmental airway, aliquots of sterile saline was instilled in to through the scope, allowing sampling of inflammatory cells. Recovery of cells enables identification of type of cells and presence of active alveolitis, type and chronicity of inflammation in the lower respiratory tract. In the study BAL study was performed in 43 cases. Lavage fluid was examined by pathologist for the type of inflammatory cells. The differential cell count including neutrophils, eosinophils, macrophages, and lymphocytes were analyzed.

Rheumatoid Factor

Rheumatoid factor estimation was done with latex agglutination method. The test was considered to be positive if the RF tirer exceeded 1:40 dilution.

Antinuclear Antibody

Antinuclear antibody screening was done by Elisa method (Calbiotech INC.). ANA screen Elisa test system is an enzyme – linked Immunosorbent assay (ELISA) for the detection of IgG class antibodies to ANA in human serum. Antinuclear antibodies are frequently present in patients with systemic sclerosis. The ANA positivity in scleroderma is up to 97%. ANA Elisa is used as a screening procedure for different autoimmune disorders.

Principle of the test

Diluted patient serum is added to wells coated with purified nuclear antigens. ANA IgG Specific antibody if present, binds to the antigen. All unbound materials are washed away and the enzyme conjugate is added to bind to the antibody-antigen complex, if present. Excess enzyme conjugate is washed off and the substrate added. The plate is incubated to allow the hydrolysis of the substrate by the enzyme. The intensity of the color generated is proportional to the amount of IgG specific antibody in the sample.

Scl-70 autoantibody

Scl-70 antibody was detected with Elisa (Calibotech INC) .This test system is an enzyme linked immunosorbent assay (Elisa) for the detection of IgG class antibodies to Scl-70 in human serum or plasma. Scl-70 IgG antibodies react with human topoisomerase-I of 100 kd fragment. Scl-70 antibodies are present in 20-40% of diffuse scleroderma and in about 20% of patients with limited scleroderma. Scl-70 antibodies are sometimes reported in classical SLE without features of scleroderma, which may explain the unexpected coexistence of marker auto antibodies for SLE and Scleroderma. Some patients with silica associated systemic sclerosis have Scl-70 antibodies. The test is carried out with negative control, positive control, and calibrator is used.

Statistical Analysis :

Statistical analysis was done using SPSS Software and the results were interpreted.

RESULTS

Sixty three patients who satisfied the American college of rheumatology criteria for the classification of systemic sclerosis were subjected to various clinical and laboratory investigations including PFT, echocardiography, HRCT, and bronchoalveolar lavage study.

The 63 patients were divided in to 2 groups as to whether they belong to diffuse cutaneous or limited cutaneous systemic sclerosis.

Age, sex and disease duration

Out of 63 patients there were 5 males and 58 females. The mean age was 37 in males and 35 in females

TABLE: 1

	No. cases	**Mean**	**SD**	**t-test**
Male	5	37.20	12.931	t = 0.23 P = 0.69 Not significant
Female	58	35.33	10.088	

The age range was **17** to **60** years. The maximum number of cases occurred in the 25 to 40 age group. The female to male ratio was 15:1 (Figure 1). The maximum number of cases occurred in the age group of 25 to 40 Years.

TABLE: 2 Cardiovascular features in diffuse and limited SSc

Cardiac features		Diffuse		Limited		Significance
		n	%	n	%	
Raynaud's	Positive	13	59.1%	30	73.2%	χ^2=1.31 P = 0.25 Not significant
	Negative	9	40.9%	11	26.8%	
Palpitation	Present	5	22.7%	5	12.2%	χ^2 = 1.18 P = 0.28 Not significant
	Absent	17	77.3%	36	87.8%	
Chest Pain	Present	5	22.7%	5	12.2%	χ^2 = 1.18 P = 0.28 Not significant
	Absent	17	77.3%	36	87.8%	
Dyspnea	Present	7	31.8%	7	17.1%	χ^2 = 1.80 P = 0.18 Not significant
	Absent	15	68.2%	34	82.9%	
Syncope	Yes	2	9.1%	2	4.9%	χ^2 = 0.43 P = 0.51 Not significant
	No	20	90.9%	39	95.1%	
BP	N	19	86.4%	39	95.1%	χ^2 = 1.50 P = 0.22 Not significant
	HT	3	13.6%	2	4.9%	
JVP	N	20	90.9%	38	92.7%	χ^2 = 0.06 P = 0.80 Not significant
	R	2	9.1%	3	7.3%	
P2	N	20	90.9%	37	90.2%	χ^2 = 0.01 P = 0.93 Not significant
	L	2	9.1%	4	9.8%	
ECG	Nor	11	50.0%	27	65.9%	χ^2 = 1.50 P = 0.22 Not significant
	Abn	11	50.0%	14	34.1%	

An analysis cardiovascular features showed that the Raynaud's phenomenon was noted in 13(59%) (Figure 2) of diffuse type while it was noted in 30(73%) of limited cutaneous SSc. palpitation in 5(22%) of diffuse and 5(12%) of limited, chest pain 5(22%) of Diffuse and 5(12%) of limited, dyspnea in 7(31%) of diffuse and 7(7%) of limited, Hypertension in 3(13%) of diffuse and 2(5%) of limited type.

TABLE: 3 Cardiovascular features

The following cardiovascular features were observed in all the cases. The percentage of the features is as follows.

		n	%
Raynaud's	Positive	43	68.3%
	Negative	20	31.7%
Palpitation	Present	10	15.9%
	Absent	53	84.1%
Chest pain	Present	10	15.9%
	Absent	53	84.1%
Dyspnea	Present	14	22.2%
	Absent	49	77.8%
Syncope	Yes	4	6.3%
	No	59	93.7%
BP	N	58	92.1%
	HT	5	7.9%
JVP	N	58	92.1%
	R	5	7.9%
P2	N	57	90.5%
	L	6	9.5%
ECG	Nor	38	60.3%
	Abn	25	39.7%

Raynaud’s phenomenon occurred overall in 43 (68.3%) cases (Figure 21). Palpitations were present in 10 (15%) of cases. Chest pain was present in 10(15%) of cases. Dyspnea was present in about 14 (22%) of cases. Syncope was present 4(6%) of cases. Blood pressure was normal in 58(92%) of cases. Hypertension was noted to be present in 5(7%) of cases. JVP was normal in 58(92%) of cases and it was raised in 5(8%) cases. Pulmonary component of the second heart sound was loud in 6(10%) cases while it was normal in 57(90%) cases (Figure 3).

Resting 12 lead ECG showed normal pattern 38 (58%) cases. Low voltage QRS complex in 3(4%), intraventricular conduction disturbances in 11% (Figure 15), right bundle branch block in 5% (Figure 13), PR prolongation in 4%, left ventricular hypertrophy in 3% and left bundle Branch block in 2% and left anterior fascicular block in 1% of cases.

TABLE 4: Echocardiographic features

Valid	Frequency	Percent
CMP+PHT	1	1.6
Mld. PHT	4	6.3
Mod. PHT	10	15.9
Mod. PHT RCMP	1	1.6
MVP. MR	3	4.8
Normal	40	63.5
PHT+TR	1	1.6
Severe PHT	2	3.2
Small ASD	**1**	**1.6**
TOTAL	**63**	**100.0**

Echocardiographic evaluation was done in all the 63 cases (Figure 4). 40(64%) cases revealed normal echocardiographic features. Mild PHT was noted in 4(6%) of cases. Moderate pulmonary hypertension was observed in 10(16%) cases. PHT with tricuspid regurgitation was noted in 1 case. Severe PHT was present in 2(3%) cases (Figure 9). Non of the control subjects had any evidence of pulmonary hypertension. Small atrial septal defect (ASD) was seen as a coincidental finding in 1 case (Figure 11).

TABLE: 5 Pulmonary features

Cough	No	42	66.7%
	Yes	21	33.3%
BOE	No	40	63.5%
	Yes	23	36.5%
Pleu.Pain	No	55	87.3%
	Yes	8	12.7%
PneumoThorax	No	62	98.4%
	Yes	1	1.6%
Velcro	No	38	60.3%
	Yes	25	39.7%

Cough was present in 21(33%) of cases. Breathlessness on exertion was noted in 23(36%) of cases. Pleuritic chest pain in 8(13%) , pneumothorax in 1 case. Velcro crackles were observed by auscultation in 38(60%) cases.

TABLE: 6 Pulmonary investigations

PFT	N	39	61.9%
	Mild R	2	3.2%
	MR	12	19.0%
	SR	10	15.9%
CXR	Nor	43	68.3%
	Pos	20	31.7%
BAL	Neg	26	61%
	Pos	17	39%
HRCT	ILD	28	44.4%
	Nor	35	55.6%

Pulmonary function testing revealed normal spirometric parameters in 39(61%) of cases. Mild restriction was noted in 2(3%) cases. Moderate restriction was seen in 12(19%) cases. Severe restriction was noted in 10(15%) cases. Chest radiography showed reticulonodular pattern suggestive of interstitial lung disease in 20(31%) cases (Figure 10). Broncho alveolar lavage analysis was suggestive of ILD in 17(39%) cases (Figure 5).

HRCT revealed features consistent with ILD in 28(44%) cases (Figures 9 & 11).

HRCT findings included ground glass opacity, increased pleural thickening, fine reticular pattern, honey combing and mixed reticular and honey compang. Inter and intra lobular septal thickening was also noted. HRCT lower lung zone distribution was predominant.

TABLE 6A: HRCT Findings on HRCT of Chest

Feature	No. of Cases	Percentage
Ground glass opacity	7	25%
Pleural thickening	4	14%
Fine reticular pattern	2	7%
Interlobular thickening	4	14%
Intralobular thickening	3	11%
Honey combing	3	11%
Mixed pattern	3	11%
Features of extensive fibrosis	2	7%

TABLE: 7 Primary and secondary PHT

PPHT	No	56	88.9%
	Yes	7	11.1%
SPHT	No	53	84.1%
	Yes	10	15.9%
RF	Neg	45	71.4%
	Pos	18	28.6%
ANA	Neg	21	33.3%
	Pos	42	66.7%
Scl70	BLP	7	11.1%
	HP	16	25.4%
	MP	12	19.0%
	Neg	28	44.4%

Primary pulmonary hypertension was noted to be present in 7(11%) cases (Figure 6). Secondary Pulmonary hypertension was observed in 10(16%) cases (Figure 7).

TABLE: 8 Secondary PHT in diffuse and limited subtypes

Diffuse/Limited			HRCT					Significance
			ILD		Nor		n	
			n	%	n	%		
D	SPHT	No	6	54.5%	11	100.0%	17	$\chi 2$=6.47 P=0.01 significant
		Yes	5	45.5%			5	
	Group Total		**11**	**100.0%**	**11**	**100.0%**	**22**	
L	SPHT	No	12	70.6%	24	100.0%	36	$\chi 2$=8.04 P=0.005 significant
		Yes	5	29.4%			5	
	Group Total		**17**	**100.0%**	**24**	**100.0%**	**41**	

Secondary PHT due to interstitial lung disease was observed in 5(45%) of total of 10 cases in limited cutaneous type. The other 5 cases of secondary pulmonary hypertension had diffuse cutaneous type with interstitial lung disease.

TABLE: 9 X ray and HRCT correlation

CXR	Nor	44	85.5%	$\chi 2$=30.33 P=0.001 Significant
	Nor	19	14.5%	
HRCT	Nor	35	55.6%	
	Pos	28	44.4%	
Group Total		**63**	**100.0%**	

Conventional chest skiagraphy showed features consistent with interstitial lung disease, in 19(44%) cases while HRCT showed features of ILD in 28(44%) cases

TABLE: 10 Distribution of pulmonary features

Pulmonary features		Diffuse		Limited		Significance
		n	%	n	%	
Cough	No	12	54.5%	30	73.2%	χ^2=2.23 P=0.13 Not significant
	Yes	10	45.5%	11	26.8%	
BOE	No	12	54.5%	28	68.3%	χ^2=1.17 P=0.28 Not significant
	Yes	10	45.5%	13	31.7%	
Pleu. Pain	No	19	86.4%	36	87.8%	χ^2=0.03 P=0.87 Not significant
	Yes	3	13.6%	5	12.2%	
Pneumo Thorax	No	22	100.0%	40	97.6%	χ^2=0.55 P=0.46 Not significant
	Yes	0	0%	1	2.4%	
Velcro	No	11	50.0%	27	65.9%	χ^2=1.50 P=0.22 Not significant
	Yes	11	50.0%	14	34.1%	
PFT	Mild R	0	0%	2	4.9%	χ^2=2.61 P=0.46 Not significant

Cough was seen in 10(45%) in diffuse type and 11(27%) in limited cutaneous type. Breathlessness on exertion was seen in 10(45%) in diffuse cutaneous type and 13(31.7%) in limited type. Pleuritic chest pain in 3(13%) of diffuse and 5(12%) of limited type. Pneumothorax was noted in 0% of diffuse and 1 case in limited cutaneous type. Velcro crackles were seen in 11(50%) of diffuse and 14(34%) of limited type.

X Ray chest was positive for ILD in 9 out of 22 cases (40%) in diffuse cutaneous type and 11 of 41(26%) of limited cutaneous type. X Rays showed reticulonodular pattern in all this cases. BAL was positive in13 out of 22(59%)cases of diffuse type and 13(31%) of limited type.

HRCT was consistent with ILD in 11 out of 22 cases of diffuse and 17 of 41(41%) of Diffuse type.

TABLE: 12 Secondary PHT and subtypes

Diffuse/Limited			HRCT					Significance
			ILD		Nor		n	
			n	%	n	%		
D	SPHT	No	6	54.5%	11	100.0%	17	$\chi 2$=6.47 P=0.01 significant
		Yes	5	45.5%			5	
	Group Total		**11**	**100.0%**	**11**	**100.0%**	**22**	
L	SPHT	No	12	70.6%	24	100.0%	36	$\chi 2$=8.04 P=0.005 significant
		Yes	5	29.4%			5	
	Group Total		**17**	**100.0%**	**24**	**100.0%**	**41**	

Secondary PHT was present in 5 out of 22 diffue and 5 out of 41 limited cutaneous types

TABLE: 13 Scl-70 positivity

Scl-70	BLP	1	3.6%	6	17.1%	$\chi 2$=3.75 P=0.29 Not significant
	HP	8	28.6%	8	22.9%	
	MP	7	25.0%	5	14.3%	
	Neg	12	42.9%	16	45.7%	
Group Total		**28**	**100.0%**	**35**	**100.0%**	

Scl 70 positivity was noted as a whole in 35 cases (Figure 8). Border line positivity was seen in 1 out of 28 cases in diffuse type, 6 of35 cases of limited type, moderate positivity 7 of 28 cases of diffuse and 5 of 35 limited type and high positivity in 8 of 28 cases of diffuse and 8 cases of 35 cases of limited cutaneous type.

TABLE: 14 Rheumatoid factor positivity

Positive	18	28.6
Negative	45	71.4
Total	**63**	**100.0**

Out of total cases of 63, 18 (29%) had seropositivity for Rheumatoid factor

TABLE:15 ANA auto antibody in SSc

	Frequency	**Percent**
Positive	42	66.7
Negative	21	33.3
Total	**63**	**100.0**

42 (63%) patients have ANA positivity done by indirect immunoflourescence.

DISCUSSION

Systemic sclerosis occurs predominantly in females. Various studies show the female to male ratio to be 3 to 14:1. This study showed a sex ratio of 15:1. Age of disease occurrence of systemic sclerosis is in the range of 30-50 years whereas this study showed an age range of 17-60 years. The mean age of onset in white men and women are 44 and 42. This study showed a mean age of 37 years in males and 35 years in females. Mean age of onset among African American men and women are 41 and 38 years.

90% of patients with systemic sclerosis have Raynaud's phenomenon. 68% of patients of this study had Raynaud's phenomenon. Raynaud's phenomenon occurred in 59 % of patients of diffuse type and in 73 % of limited type. Palpitation occurred in 10 (15.9%) cases. Palpitations occur both in primary and secondary forms of pulmonary hypertension. Cardiac involvement can occur in the form of myocardial involvement, conduction system abnormalities, arrhythmias or pericardial disease.

Systemic sclerosis can involve the myocardium, pericardium, and conduction sytem of the heart (36). Dyspnea is common, paroxysmal nocturnal dyspnea and orthopnea can occur if myocardial involvement is advanced. Pulmonary hypertension can present with features of right heart failure. Palpitations either due to brady or tachy arrhythmias or just a perceived bounding of the heart beat in sinus rhythm, are common.

Atypical chest pain is common but classical angina and myocardial infarction may occur with normal epicardial coronary arteries. Cardiac involvement in SSc is

clinically occult often and reports of prevalence of cardiac disease vary depending on the methods used to identify it. Recent studies suggest that clinical evidence of myocardial disease may be seen 20 to 25% of patients with SSc.

Follansbee et al through autopsy studies have found cardiac involvement particularly myocardial fibrosis and pericardial disease are frequent. The prevalence of myocardial fibrosis varies between 30-81% in various series. (37) Echocardiographic screening of SSc patients has found a high prevalence of asymptomatic cardiac abnormalities.

Smith et al noted that in a study of 54 patients 22(41%) had pericardial effusion by echocardiography. Echocardiographic abnormalities have been recorded in up to 69% of cases. Patients with palpitations often have atrial or ventricular ectopy. If the cardiac involvement becomes clinically manifest, it portends an adverse prognosis.

Medsger and Masi et al predicted clinical cardiac disease in SSc was associated with 70% mortality at 5 years (38). Left axis deviation and moderate or large pericardial effusion were the two variables to independently predict mortality (39).

As new cardiac technologies evolve many asymptomatic cardiac abnormalities may be noted. Long term studies are necessary to determine the outcome and the best approach to the treatment of such abnormalities. Diastolic dysfunction has been noted to be more common in recent years. Right ventricular diastolic dysfunction seen in 8 patients and left ventricular diastolic dysfunction occurred in 4 patients.

When comparing Echo and Doppler differences between patients with SSc and controls there was a significant difference between the two groups regarding the right ventricular cardiac chamber dimensions. There was a significant difference in the estimated pulmonary artery systolic pressure between patients with and without ventricular diastolic dysfunction.

Diastolic dysfunction of RV, LV or both can occur in SSc, which can occur with or without the presence of pulmonary hypertension or systemic hypertension. More often it is asymptomatic. The extent of the RV diastolic dysfunction was not related to the duration of the disease or to the skin score.

Initial cardiac evaluation at presentation with resting 12 lead ECG in 63 patients revealed normal pattern 58.7% of cases (37 cases). Low voltage QRS complexes were noted in 3 cases (4.8%). Intra ventricular conduction disturbances and right bundle branch block were noted in 11.1% and 4.8% (7&3 cases). PR prolongation as an isolated abnormality was seen 4.8% (3) cases. Left ventricular hypertrophy was seen in 2 cases. Left bundle branch block and left anterior fasicular block were seen in 1 case each.

Follansbee WP et al in their review of 436 patients have noted the prevalence of abnormalities of on resting ECG which revealed normal ECG in 56%, PR prolongation in 5%, RBBB in 2%, LBBB in 1%, LAFB in 5%, intraventricular conduction disturbances in 4%, LVH in 7% and non specific ST –T wave abnormalities in7% and low voltage QRS in 5% of cases.

Patchy myocardial fibrosis and conduction system disease in SSc patients form a substrate for the generation of supraventricular and ventricular arrhythmias (40). Cardiac involvement in SSc is often clinically occult and hence reports of the prevalence of cardiac disease vary depending upon methods used to define this entity. It is increasingly recognized that significant pulmonary arterial hypertension in more than 15% of patients with SSc. As this complication can occur even in the absence of overt interstitial lung disease (Isolated PAH), it has been linked to primary PAH and is attributable to intrinsic vascular pathology that is the hallmark of SSc.

Deregulatory activity of mediators controlling vasomotor tone has been implicated, and the level of endothelin-1 (ET-!) are elevated in the circulation and in the lung. Enhanced vasoconstriction, vascular endothelial proliferation, smooth muscle hypertrophy and irreversible vascular remodeling in lung, ET-1 appears to play a role in pathogenesis.

SSc is often associated with pulmonary hypertension. Although patients with limited cutaneous type are more likely to develop PHT than those with diffuse form of SSc, the true prevalence of PHT in SSc and the risk factors associated with its development are unknown .Primary pulmonary hypertension occurred in 7(11%) of cases and secondary PHT in 10 (15.9) cases. Because the prognosis of patients with SSc associated with PHT is substantially worse than that of patients without this complication, intensive efforts are underway to develop sensitive screening strategies and effective treatment. Serial evaluation of SSc patients with Doppler echocardiography appears to be prudent (41). Most studies differentiate scleroderma

associated PHT and ILD as a two separate pathologies concentrating on one or the other; however, many patients have both problems.

Chang et al in a retrospective cross sectional study of 614 patients with SSc who had echocardiography and PFT performed within 6 months of one another. Echocardiography determined presence of pulmonary hypertension and PFT documented Restrictive ventilatory defect (RVD). 22.5% had isolated RVD; 19.2% had isolated PHT; 18.1% had both combined RVD and isolated PHT. The individuals with combined RVD and PHT resembled patients with isolated RVD in that they had a high prevalence of diffuse skin involvement and antitopoisomerase positivity. 39.2% patients with mild RVD and 51.4% of severe RVD had pulmonary hypertension(42).

De Azevedo AB et al have noted a prevalence of 28% in a study of 16 patients(43).

Chang et al used a cohort of 1136 SSc patients predicted the risk factor for pulmonary hypertension which include older age, limited skin disease, and elevated pulmonary artery pressures at the time of initial evaluation (44)

In another study **Stupi et al** assessed the occurrence of pulmonary hypertension in CREST syndrome. They reported 59 of 673 CREST syndrome patients had PHT.

Koh ET et al analyzed retrospectively 344 patients with SSc followed prospectively for the occurrence of PHT. 17 (4.9%) were found to have PHT. 8 had

isolated PHT while 9 had PHT secondary to ILD. Patients with RVD developed PHT earlier but the survival was better that of PHT.

A patient with limited cutaneous SSc presented with acute breathlessness with congestive cardiac failure and she was found to have biventricular dysfunction with dilated cardiomyopathy and moderate pulmonary hypertension. There was complete recovery with reversal of PHT and biventricular function normalized after 3 months. This illustrates the occurrence reversible cardiomyopathy due to disturbances of microcirculation of the heart vessels, probably due to systemic Raynaud's phenomenon. This might have resulted in transient, persistent microcirculatory disturbances causing ventricular dysfunction and cardiomyopathy.

The literature pertaining to the interstitial lung disease indicates that it is a major contributor of morbidity and mortality. The clinical approach to staging of the disease activity remains controversial. High resolution computed tomographic scans, broncho alveolar lavage, and various serum markers (e.g., surfactant protein D and KL-6) each may provide useful information about the degree of activity of the systemic sclerosis- interstitial lung disease.(45). Abnormalities of lung function occur in 70% of patients with systemic sclerosis. Screening of patients recently diagnosed with SSc by pulmonary function tests and HRCT identify a significant number of patients with early asymptomatic fibrosing alvoelitis in systemic sclerosis (FASSc)(46).

Interstitial lung disease associated with SSc is seen in diffuse disease, though it can be present in limited disease also. The nonspecific nature of SSc associated ILD

makes it different from idiopathic ILD and helps to explain its better prognosis. ILD is one of the leading two causes of death in SSc. (47).

Dyspnea in scleroderma patients can be due to chest wall tightening and skin involvement, pleural disease, cardiac involvement, myositis of intercostals muscles, or due to scleroderma lung disease. Scleroderma lung disease encompasses vascular (PHT) or ILD or both. A comprehensive work up is required to delineate the underlying cause of dyspnea in a scleroderma patient, and to establish the contribution of each component to symptoms. (48). Pulmonary function tests play a vital role in the evaluation of Patients with systemic sclerosis and for assessing the presence and the severity of SSc lung involvement. But they have got limitations as patients with severe skin disease might encounter problems in performing the tests. However they play a crucial role in the evaluation of lung function in the early disease. X ray of the chest is least sensitive in indicating the lung abnormalities but it does have role in the assessment of severe disease.

The incidence of radio graphically recognizable interstitial lung disease is around 25%. The range varies from 10 to 80%. Usual interstitial pneumonia, is common form of ILD. But occasionally non-specific interstitial pneumonia (NSIP) also occurs. The HRCT findings of interstitial lung disease in SSc are honey combing, irregular reticulation, sub pleural lines, ground glass opacity, consolidation, and a subpleural distribution.

Chan et al compared the HRCT findings of 52 patients with idiopathic pulmonary fibrosis with 52 patients of SSc with ILD. He concluded that the patients with SSc have fine reticular pattern and less upper Zone involvement.

Schurawitzki et al studied 23 patients with SSc. HRCT findings include subpleural lines (74%), septal thickening or parenchymal bands(43%) and honeycombing(43%). Honeycombing had uniform or peripheral distribution. Parenchymal abnormalities had upper lung to middle lung to lower lung distribution ratios of 1:2.4:3.8, conforming the typical lower lung zone predominance or abnormalities.

Remy-jardin et al reviewed the HRCT, PFT and BAL results of 53 patients with SSc emphasizing the frequency of honey combing and ground glass opacity. These abnormalities have a basal, posterior and peripheral predominance. Small nodules with or without honeycombing is reported. HRCT ground glass opacity indicates reduction in diffusing capacity while honeycombing indicates reduction in lung volumes and diffusing capacity. Increased pleural thickening, esophageal dilatation, in 40 to 60% of patients.

Predominant ground glass appearance correlates with alveolitis and reticular pattern correlate with presence of fibrosis in pathogenic specimens. Out of 28(44%) patients who had ILD by HRCT 12 had ground glass opacities, 8 had fine reticular pattern 4 had features of honey combing and 4 had mixed findings of reticular and extensive honeycombing. In this study BAL identified ILD in 41% of patients whereas HRCT could identify 44% of patients with interstitial lung disease.

CONCLUSION

1. Systemic sclerosis is common in females and the female: male ratio is 15:1, with an age range of 17 to 60 years with a mean age of 37 in males and 35 in females.

2. Limited cutaneous type of presentation is more common.

3. Raynaud's phenomenon is seen in both limited and diffuse cutaneous types, but the occurrence is more common in limited cutaneous type.

4. Secondary pulmonary hypertension due to interstitial lung is more common than the primary type of pulmonary hypertension.

5. Resting ECG revealed abnormalities in 42% of patients. ST-T wave changes followed by intra ventricular conduction disturbances constitute the most common abnormalities.

6. Mild pulmonary hypertension was noted in 6.3%, modereate pulmonary hypertension in 15.9%, and severe PHT in 3.2% of patients. Reversible cardiomyopathy was seen in 1 patient.

7. Mitral valve prolapse with or without mitral regurgitation was observed in 4.8% of patients.

8. Significant difference was noted in the right and left ventricular chamber dimensions between the patients and normal controls. The difference in the estimated pulmonary pressure was considerable in patients with and without ventricular diastolic dysfunction.

9. Chest X ray showed features of interstitial lung disease in 31.7% while HRCT revealed features of interstitial lung disease in 44.4% of individuals.

10. Pulmonary function tests showed mild restrictive type of ventilatory defect in 3.2%, moderate restriction in 19% and severe restriction in 15.9%. Normal PFT was seen in 61.9% of patients.

11. Interstitial lung disease was more common in diffuse cutaneous systemic sclerosis.

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APPENDIX - II

ABBREVIATION CODE FOR MASTER CHART

BP	**-**	**Blood pressure**
JVP	**-**	**Jugular venous pressure**
P2	**-**	**Pulmonary component of second heart sound**
ECG	**-**	**Electrocardiogram**
Echo	**-**	**Echocardiography**
BOE	**-**	**Breathlessness on exertion**
Pleu.Pain	**-**	**Pleutitic chest pain**
Velcro	**-**	**Velcro Crackles**
PFT	**-**	**Pulmonary function tests**
CXR	**-**	**X ray chest PA view**
BAL	**-**	**Bronchoalveolar lavage**
HRCT	**-**	**High resolution computed tomography**
PPHT	**-**	**Primary pulmonary hypertension**
SPHT	**-**	**Secondary pulmonary hypertension**
RF	**-**	**Rheumatoid factor**
ANA	**-**	**Antinuclear antibody**
Scl-70	**-**	**Anti Scl-70 auto antibody**

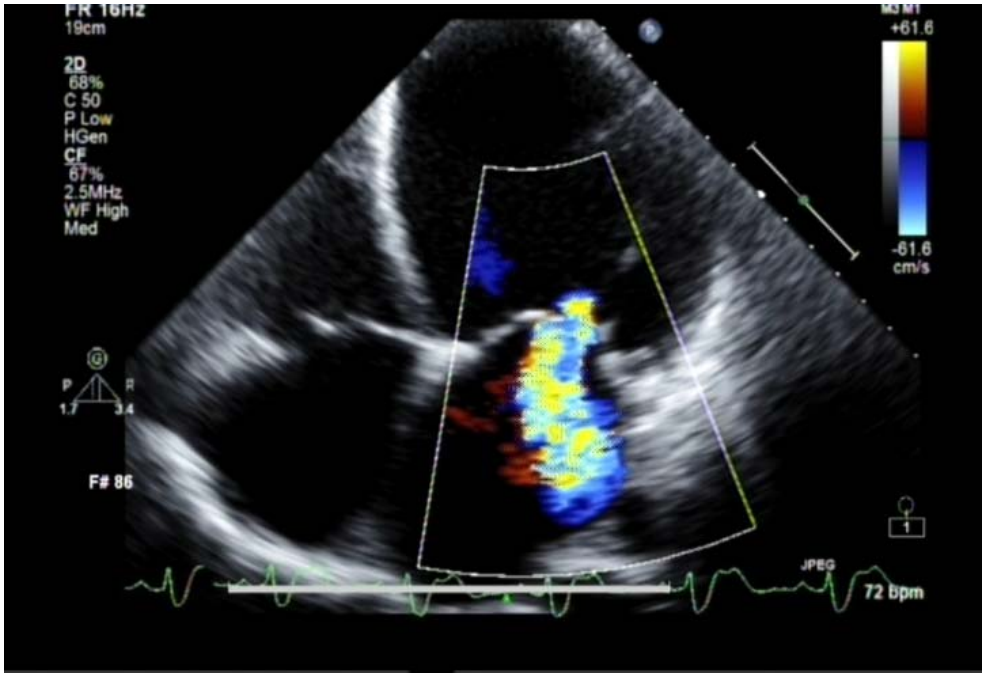


Figure 9 : Apical-4 chamber view shows features of Dilated Cardiomyopathy LA & LV dilated/MR(moderate)

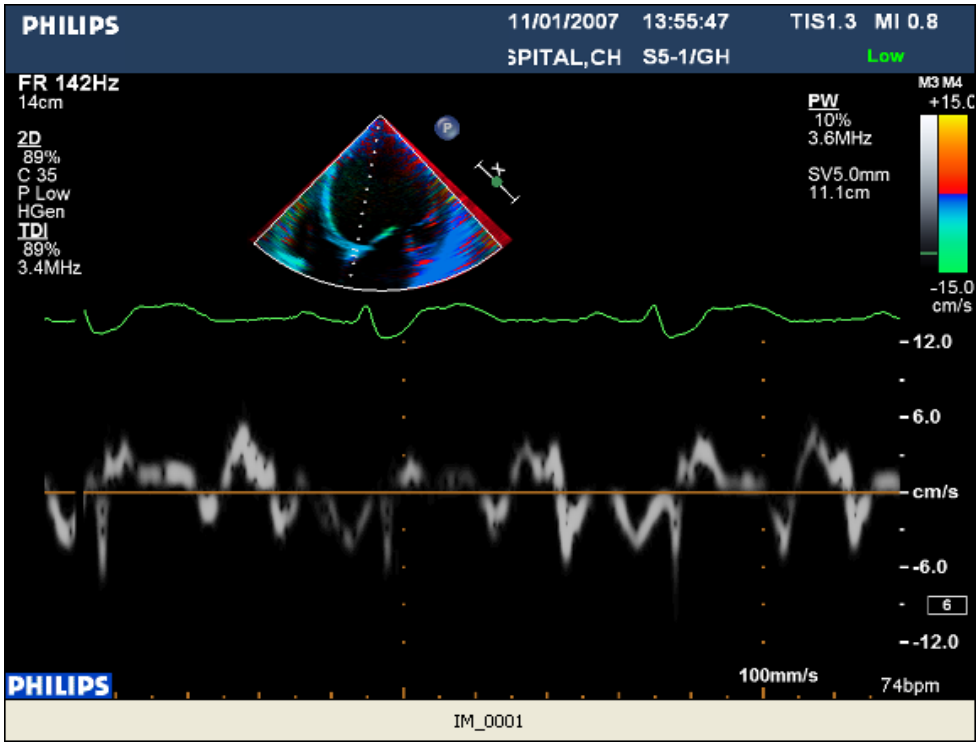


Figure 10: TDI of DCMP showing reduced septal annular motion velocity

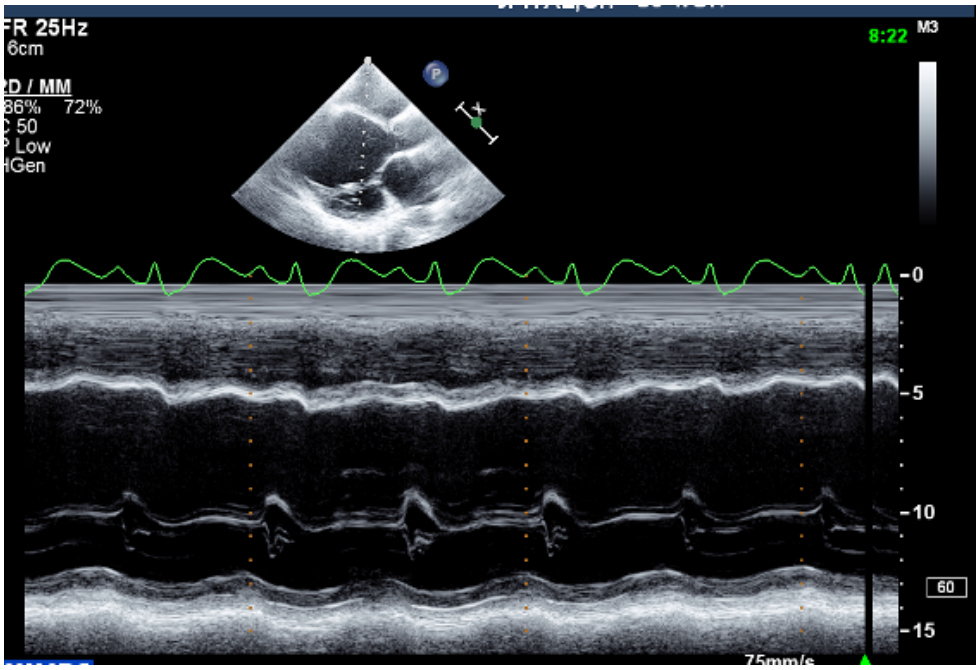


Figure 11 : M-Mode Echo of DCMP

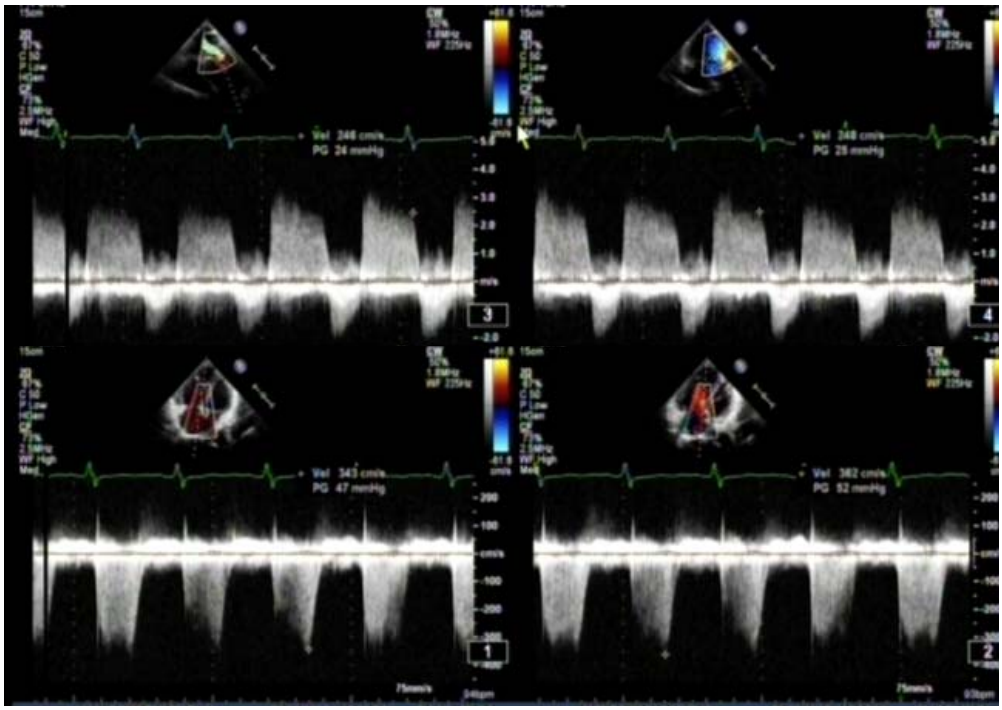


Figure 12: Echo shows continuous wave Doppler across the tricuspid valve indicating moderate PHT/ continuous wave Doppler across the pulmonary valve indicating moderate pulmonary regurgitation due to PHT

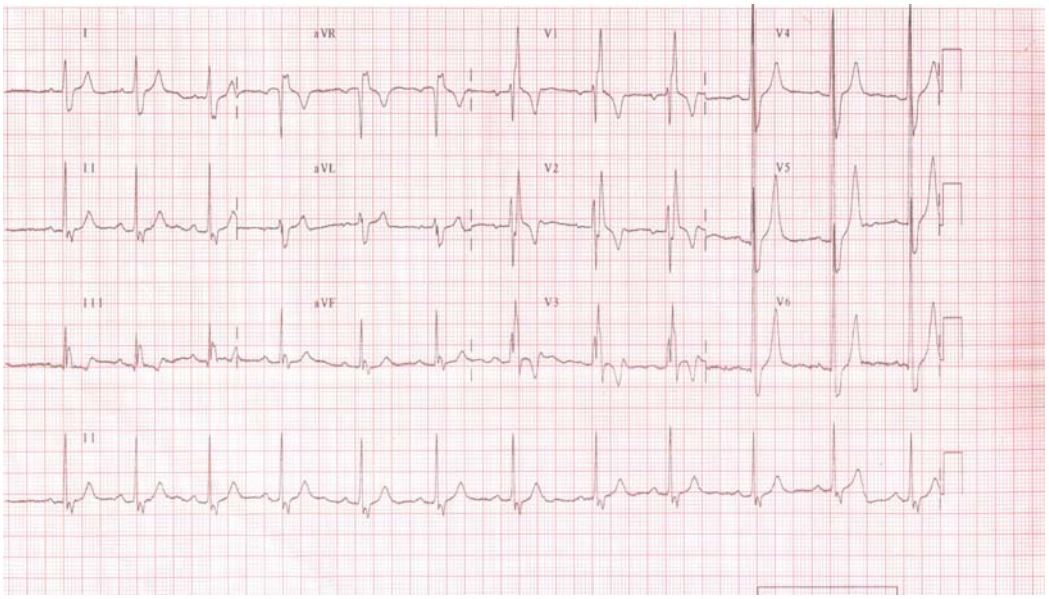


Figure 13 : 12 lead ECG showing Complete RBBB

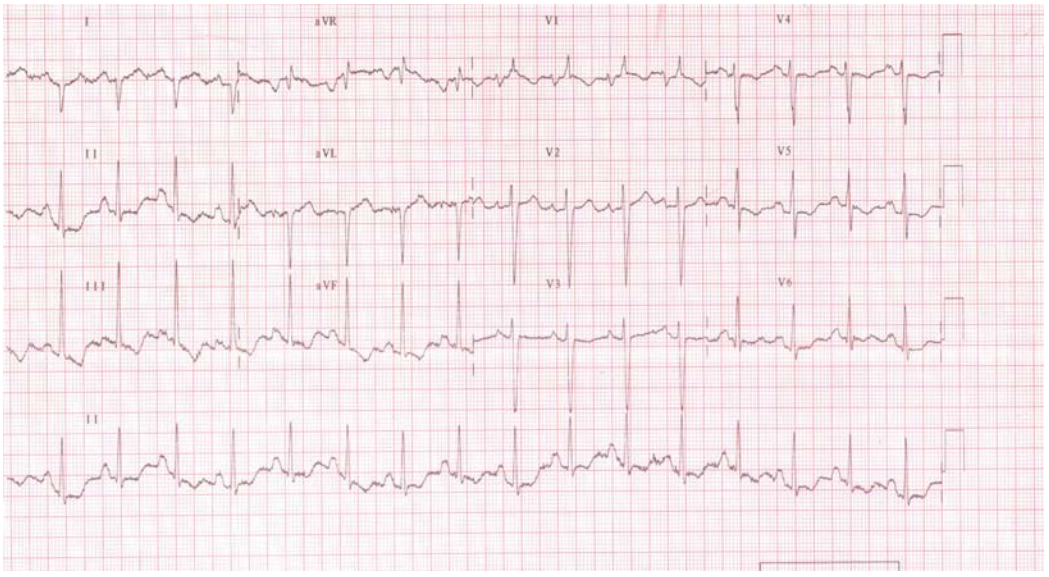


Figure 14: 12 lead ECG showing Features of Right ventricular hypertrophy

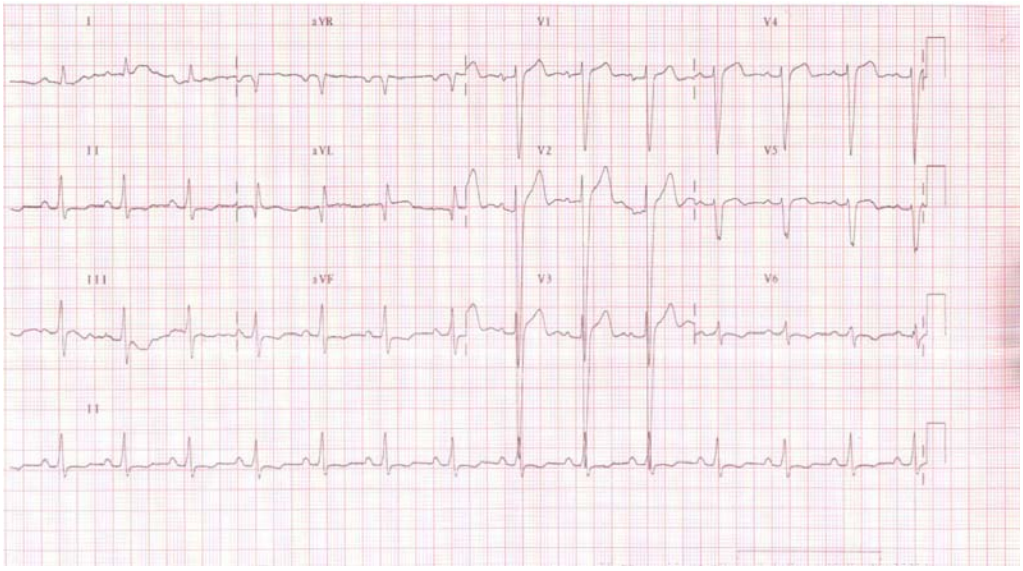
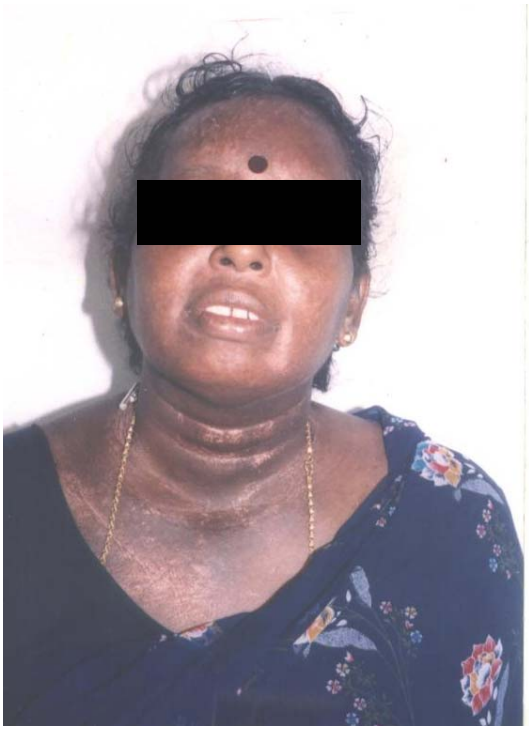


Figure 15: 12 lead ECG showing Features of Intraventricular conduction defect



Picture 16 : Picture showing diffuse cutaneous systemic sclerosis with chest involvement

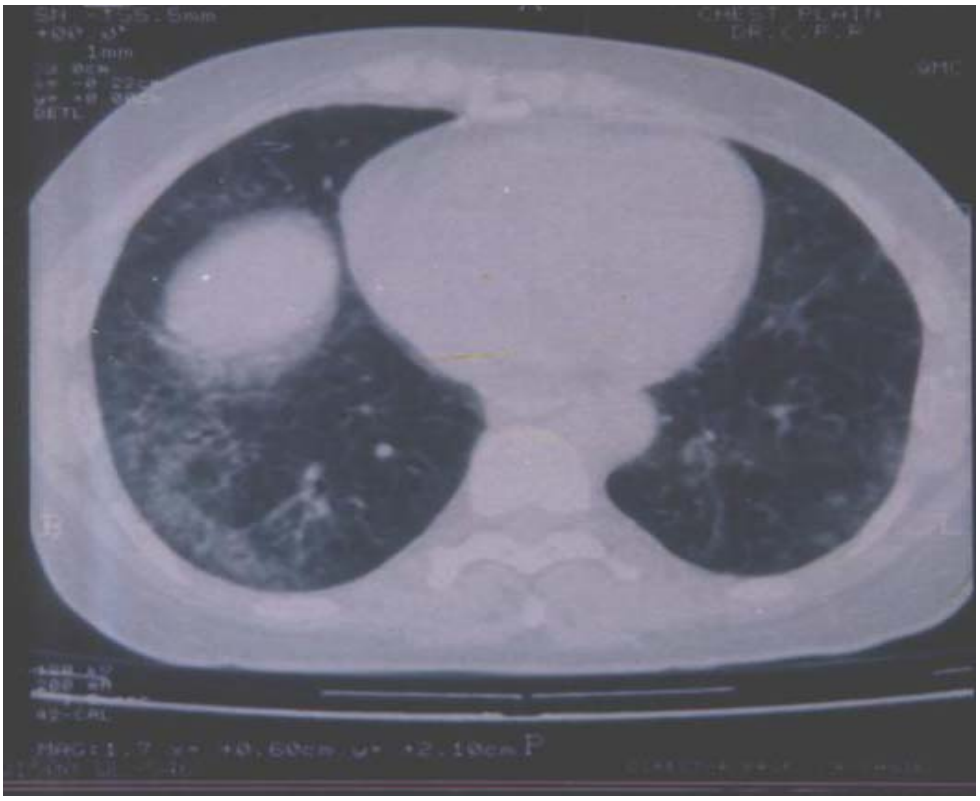


Figure 17 : HRCT showing inter ,intra lobular septal thickening and nodular opacities pattern in both lower lobes, more on the right side

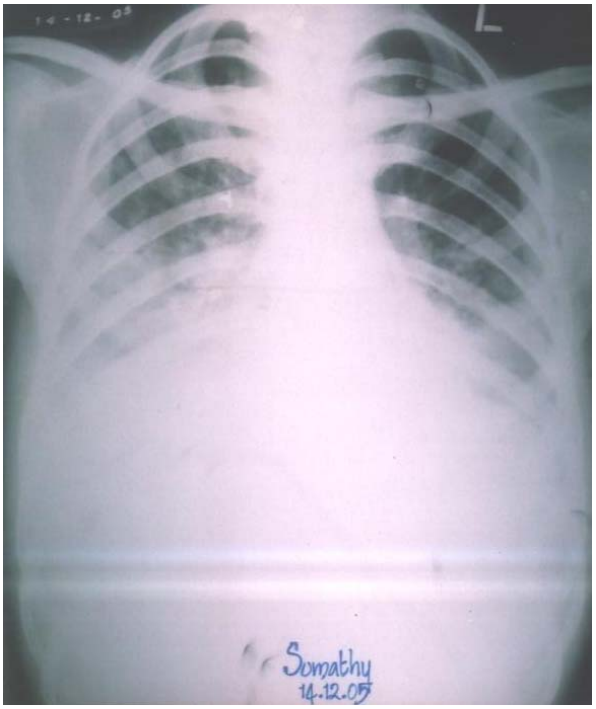


Figure 18 : X-ray chest showing bilateral reticulonodular pattern

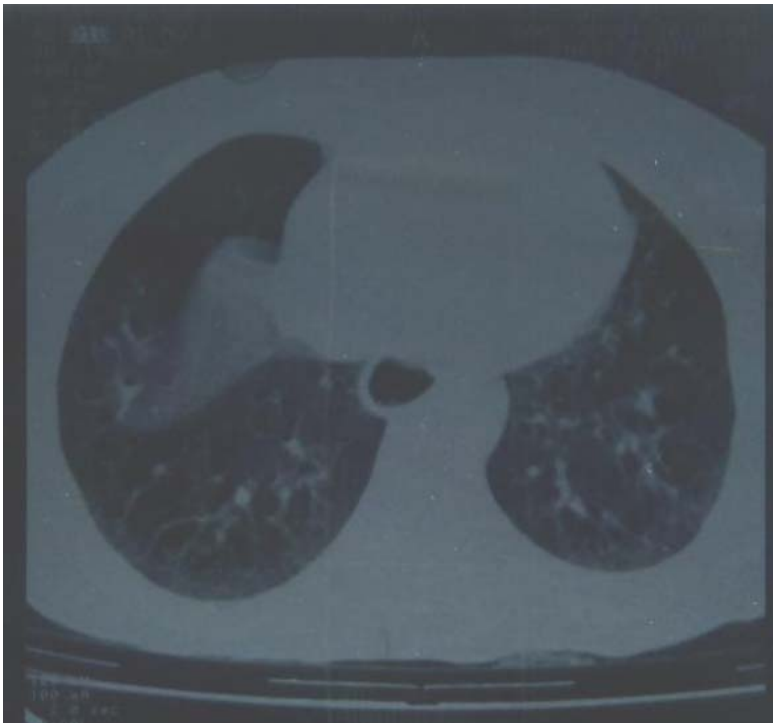


Figure 19 : HRCT lungs showing bilateral reticulonodular shadows and fibrosis

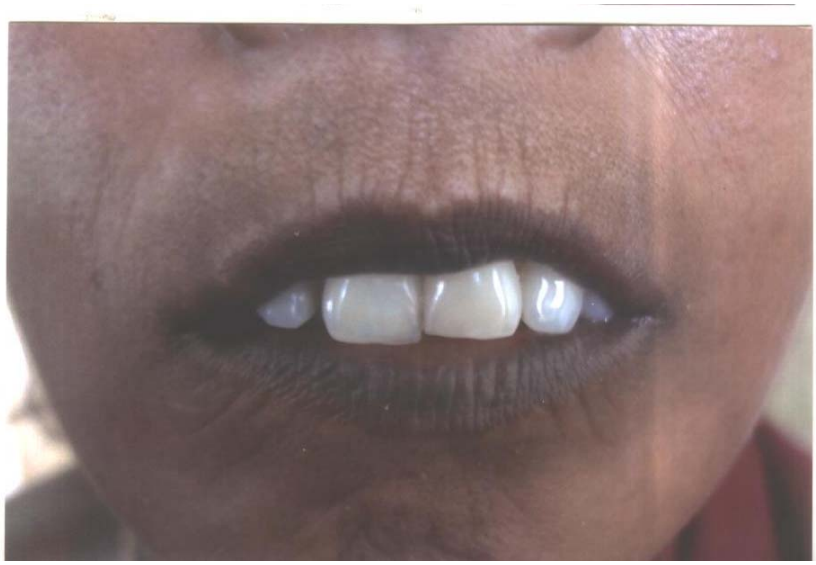


Figure 20 : Picture showing pursing of lips and characteristic facies of scleroderma

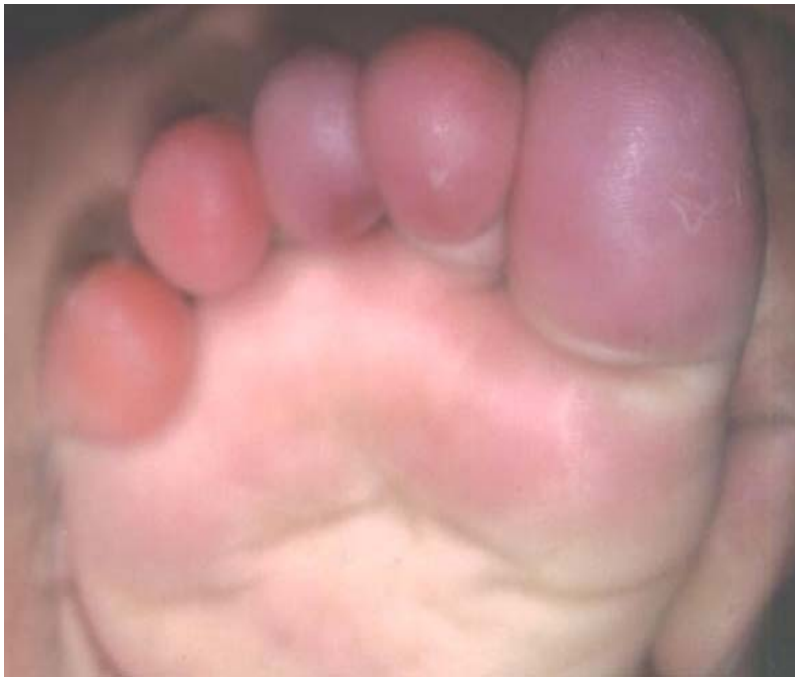


Figure 21 : Picture showing Raynaud's phenomenon

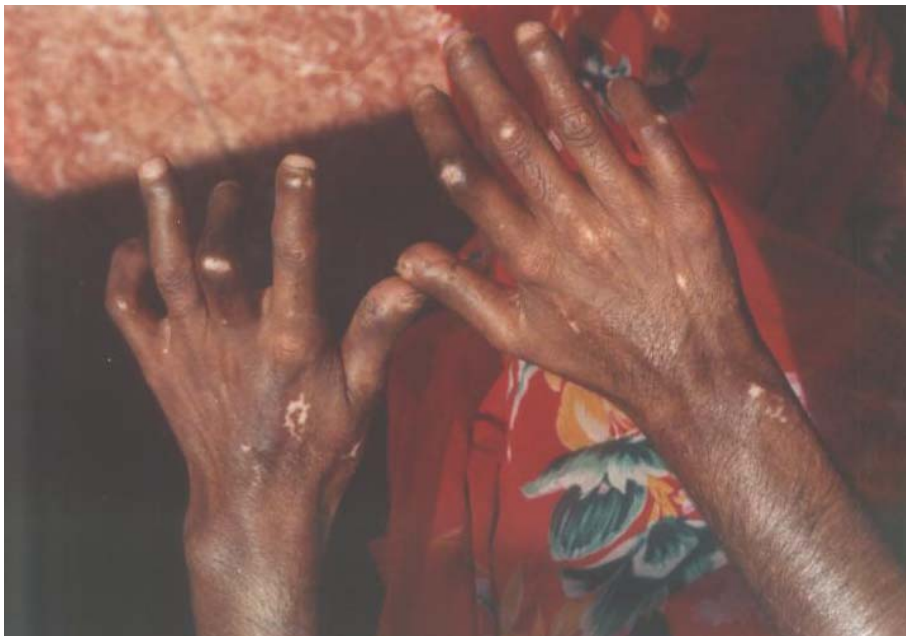


Figure 22 : Picture showing contracture and deformities of both hands. Shortening of fingers with pigmentary changes and healed ulcers over the MCP and PIP joints

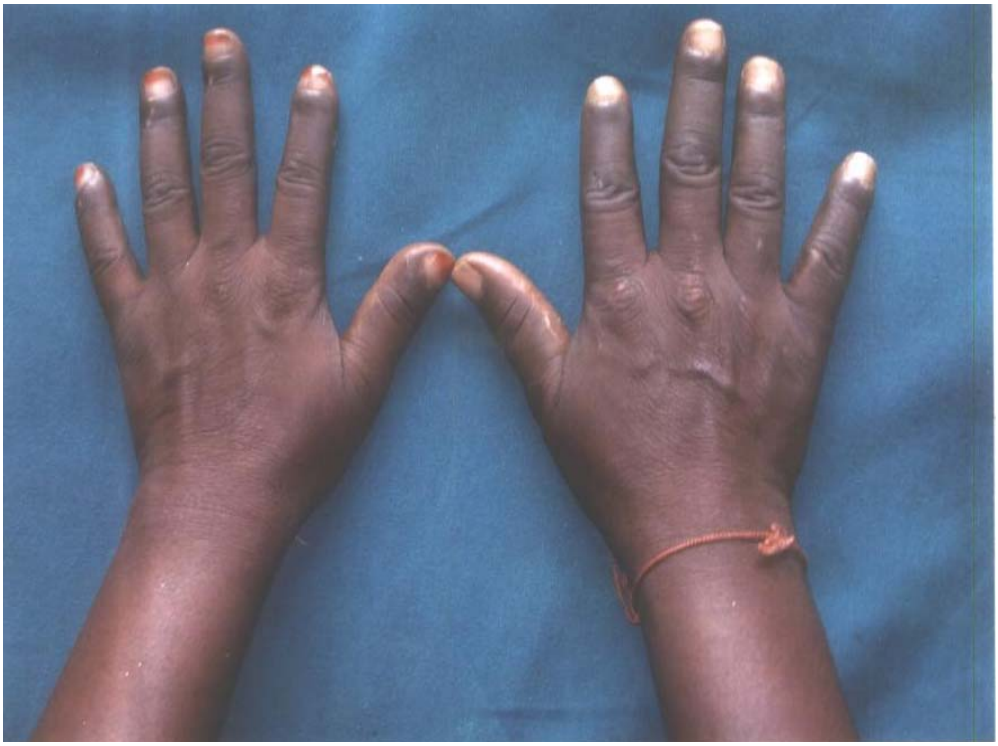


Figure 23 : Picture showing sclerodactyly

APPENDIX - I

MASTER CHART

				CARDIOVASCULAR FEATURES										RESPIRATORY FEATURES											AUTO ANTIB	
S.No	Age	Sex	Diffuse/ Limited	Raynauds	Palpitation	chest Pain	Dyspnea	Syn cope	BP	JVP	P2	ECG	Echo	Cough	BOE	Pleu. Pain	Pneumo Thorax	Velcro	PFT	CXR	BAL	HRCT	PPHT	SPHT	RF	ANA
1	22	F	D	Positive	Present	Present	Present	No	N	R	N	Abn	CMP+PHT	Yes	Yes	No	No	No	N	Nor	Neg	Nor	No	No	Neg	Pos
2	48	F	L	Negative	Absent	Absent	Absent	No	N	N	N	Nor	N	No	No	No	No	No	SR	Nor	Neg	Nor	No	No	Pos	Pos
3	55	F	D	Positive	Absent	Absent	Absent	No	N	N	N	Abn	PHT+TR	No	No	No	No	No	SR	Nor	Neg	Nor	No	No	Neg	Neg
4	31	F	L	Positive	Absent	Absent	Absent	No	N	N	N	Abn	N	No	No	No	No	No	MR	Pos	Neg	ILD	No	No	Neg	Neg
5	39	F	L	Positive	Absent	Absent	Absent	No	N	N	N	Nor	N	No	No	No	No	Yes	MR	Pos	Pos	ILD	No	No	Neg	Pos
6	40	F	D	Positive	Absent	Present	Absent	No	N	N	N	Abn	N	No	No	No	No	Yes	MR	Pos	Pos	ILD	No	No	Pos	Pos
7	40	F	L	Positive	Absent	Absent	Present	No	N	N	N	Nor	N	Yes	Yes	Yes	No	Yes	Mild R	Pos	Pos	ILD	No	No	Neg	Pos
8	42	M	D	Negative	Absent	Absent	Absent	No	N	N	N	Nor	N	No	No	No	No	Yes	N	Pos	Pos	ILD	No	No	Neg	Pos
9	33	F	D	Positive	Absent	Absent	Present	No	N	N	N	Abn	N	Yes	Yes	Yes	No	Yes	MR	Neg	Pos	Nor	No	No	Neg	Neg
10	20	F	L	Negative	Absent	Absent	Absent	No	N	N	N	Nor	N	No	Yes	No	No	Yes	N	Neg	Neg	Nor	Yes	No	Pos	Neg
11	29	F	L	Positive	Absent	Absent	Absent	Yes	HT	N	N	Abn	Mod. PHT +RCMP	Yes	Yes	Yes	No	No	N	Pos	Neg	ILD	No	No	Pos	Pos
12	30	F	L	Negative	Absent	Absent	Absent	No	N	N	N	Nor	Small ASD	No	No	No	No	Yes	N	Pos	Pos	ILD	No	Yes	Neg	Pos
13	32	F	L	Negative	Absent	Absent	Absent	No	N	N	N	Nor	Mod. PHT	No	No	No	No	Yes	N	Pos	Pos	ILD	No	Yes	Neg	Pos
14	33	M	D	Negative	Present	Present	Present	No	N	N	N	Nor	Mod. PHT	Yes	Yes	No	No	No	SR	Neg	Pos	Nor	No	No	Neg	Pos
15	50	M	D	Positive	Absent	Absent	Absent	No	N	N	N	Nor	N	Yes	Yes	No	No	No	N	Nor	Neg	Nor	Yes	No	Pos	Pos
16	45	F	D	Positive	Present	Present	Present	Yes	N	R	L	Nor	Mod. PHT	Yes	Yes	No	No	No	N	Pos	Neg	Nor	Yes	No	Neg	Pos
17	20	F	L	Positive	Present	Present	Present	No	N	R	L	Nor	Severe PHT	Yes	Yes	No	No	No	N	Nor	Neg	ILD	No	No	Neg	Pos
18	30	F	L	Positive	Absent	Absent	Absent	No	N	N	N	Nor	N	Yes	Yes	No	No	No	MR	Nor	Pos	Nor	No	No	Neg	Neg
19	29	F	D	Positive	Absent	Absent	Present	No	N	N	N	Nor	N	No	Yes	No	No	No	N	Nor	Neg	Nor	No	No	Pos	Neg
20	42	M	D	Positive	Absent	Absent	Absent	No	N	N	N	Nor	N	No	No	No	No	Yes	MR	Pos	Pos	ILD	No	No	Neg	Pos
21	30	F	L	Negative	Absent	Absent	Present	No	N	N	N	Nor	Mod. PHT	No	No	No	No	No	N	Nor	Neg	Nor	Yes	No	Neg	Neg
22	32	F	L	Negative	Absent	Absent	Absent	No	N	N	N	Abn	N	No	No	No	No	No	N	Nor	Neg	Nor	No	No	Neg	Neg
23	40	F	D	Positive	Absent	Absent	Absent	No	N	N	N	Nor	N	No	No	No	No	Yes	N	Nor	Pos	ILD	No	No	Neg	Pos
24	45	F	L	Positive	Absent	Absent	Absent	No	N	N	N	Abn	N	No	No	No	No	Yes	N	Nor	Neg	ILD	No	No	Pos	Pos
25	48	F	L	Negative	Absent	Absent	Absent	No	N	N	N	Nor	N	No	No	No	No	No	N	Nor	Neg	Nor	No	No	Neg	Pos
26	40	F	L	Negative	Present	Present	Present	No	N	N	L	Abn	Mod. PHT	No	No	No	No	Yes	MR	Nor	Pos	ILD	No	Yes	Neg	Neg
27	33	F	D	Positive	Present	Present	Present	Yes	N	N	L	Abn	Mod. PHT	No	No	No	No	Yes	MR	Pos	Pos	ILD	No	Yes	Neg	Pos
28	33	F	D	Negative	Present	Absent	Present	No	N	N	N	Nor	N	No	No	No	No	Yes	N	Nor	Pos	ILD	No	Yes	Pos	Neg
29	28	F	L	Positive	Absent	Absent	Absent	No	N	N	N	Nor	Mld. PHT	No	No	No	No	No	SR	Nor	Neg	Nor	No	No	Neg	Neg
30	29	F	L	Positive	Absent	Absent	Absent	No	N	N	N	Nor	N	No	No	No	No	No	N	Nor	Neg	Nor	No	No	Neg	Pos
31	36	F	L	Negative	Absent	Absent	Absent	No	N	N	N	Nor	N	Yes	Yes	No	No	Yes	N	Nor	Pos	ILD	No	No	Neg	Pos

				CARDIOVASCULAR FEATURES										RESPIRATORY FEATURES											AUTO ANTIB	
S.No	Age	Sex	Diffuse/ Limited	Raynauds	Palpitation	chest Pain	Dyspnea	Syn cope	BP	JVP	P2	ECG	Echo	Cough	BOE	Pleu. Pain	Pneumo Thorax	Velcro	PFT	CXR	BAL	HRCT	PPHT	SPHT	RF	ANA
32	24	F	L	Negative	Absent	Absent	Absent	No	N	N	N	Nor	MVP. MR	Yes	Yes	No	No	Yes	SR	Nor	Pos	ILD	No	No	Pos	Pos
33	35	F	D	Negative	Absent	Absent	Absent	No	HT	N	N	Nor	Mld. PHT	Yes	Yes	No	No	Yes	MR	Pos	Pos	ILD	No	Yes	Neg	Neg
34	23	F	D	Negative	Absent	Absent	Absent	No	HT	N	N	Nor	N	No	No	No	No	No	N	Nor	Neg	Nor	No	No	Neg	Neg
35	48	F	L	Positive	Absent	Absent	Absent	No	N	N	N	Nor	N	No	No	No	No	No	N	Nor	Neg	Nor	No	No	Pos	Pos
36	23	F	L	Positive	Absent	Absent	Absent	No	N	R	L	Abn	Mod. PHT	Yes	Yes	Yes	No	Yes	MR	Pos	Pos	ILD	No	Yes	Neg	Pos
37	28	F	L	Positive	Present	Present	Present	Yes	N	R	L	Abn	Mod. PHT	Yes	Yes	No	No	Yes	MR	Pos	Pos	ILD	No	Yes	Pos	Pos
38	32	M	L	Positive	Absent	Absent	Absent	No	N	N	N	Nor	N	No	No	No	No	No	N	Nor	Neg	Nor	No	No	Neg	Neg
39	46	F	L	Positive	Absent	Absent	Absent	No	N	N	N	Abn	N	No	No	No	No	No	N	Nor	Neg	Nor	No	No	Pos	Neg
40	25	F	L	Positive	Absent	Absent	Absent	No	N	N	N	Nor	N	No	No	No	No	No	N	Nor	Neg	Nor	No	No	Neg	Pos
41	17	F	L	Positive	Absent	Absent	Absent	No	N	N	N	Abn	N	No	No	Yes	No	No	N	Nor	Neg	Nor	No	No	Neg	Pos
42	54	F	L	Positive	Present	Absent	Present	No	N	N	N	Abn	Mod. PHT	No	No	No	No	No	N	Nor	Neg	Nor	Yes	No	Neg	Pos
43	32	F	L	Positive	Absent	Absent	Absent	No	N	N	N	Nor	Mld. PHT	No	No	No	No	No	N	Nor	Neg	Nor	Yes	No	Pos	Neg
44	47	F	L	Positive	Absent	Absent	Absent	No	N	N	N	Abn	N	No	No	No	No	No	N	Nor	Neg	Nor	No	No	Neg	Pos
45	36	F	L	Positive	Absent	Absent	Absent	No	N	N	N	Nor	MVP. MR	Yes	Yes	No	No	Yes	MR	Pos	Pos	ILD	No	No	Neg	Pos
46	55	F	D	Negative	Absent	Absent	Absent	No	N	N	N	Nor	MVP. MR	Yes	No	No	No	Yes	N	Nor	Pos	ILD	No	No	Neg	Neg
47	35	F	D	Positive	Absent	Absent	Absent	No	N	N	N	Abn	N	No	No	No	No	No	N	Nor	Neg	Nor	No	No	Neg	Neg
48	37	F	L	Positive	Present	Present	Present	No	N	N	N	Nor	Mld. PHT	No	No	No	No	Yes	N	Nor	Neg	Nor	Yes	No	Neg	Neg
49	39	F	L	Positive	Absent	Absent	Absent	No	N	N	N	Abn	N	Yes	Yes	No	No	Yes	SR	Pos	Pos	ILD	No	No	Neg	Pos
50	37	F	L	Positive	Absent	Absent	Absent	No	N	N	N	Nor	N	No	No	No	No	No	N	Nor	Neg	Nor	No	No	Pos	Pos
51	17	F	L	Positive	Absent	Absent	Absent	No	N	N	N	Nor	N	No	No	No	No	No	N	Nor	Neg	Nor	No	No	Neg	Pos
52	40	F	D	Negative	Absent	Absent	Absent	No	N	N	N	Abn	Severe PHT	Yes	Yes	Yes	No	Yes	SR	Pos	Pos	ILD	No	Yes	Neg	Pos
53	24	F	L	Positive	Absent	Present	Absent	No	N	N	N	Nor	N	Yes	Yes	Yes	Yes	No	SR	Pos	Neg	ILD	No	No	Pos	Pos
54	28	F	L	Positive	Absent	Absent	Absent	No	N	N	N	Nor	N	No	Yes	No	No	No	Mild R	Nor	Neg	ILD	No	No	Neg	Pos
55	38	F	L	Negative	Absent	Absent	Absent	No	N	N	N	Abn	N	No	No	No	No	No	N	Nor	Neg	Nor	No	No	Pos	Neg
56	38	F	L	Positive	Absent	Absent	Absent	No	HT	N	N	Abn	N	No	No	No	No	No	N	Nor	Neg	Nor	No	No	Neg	Pos
57	24	F	L	Positive	Absent	Absent	Absent	No	N	N	N	Nor	N	No	No	No	No	No	N	Nor	Neg	Nor	No	No	Neg	Pos
58	60	F	D	Positive	Absent	Absent	Absent	No	HT	N	N	Abn	N	No	No	No	No	No	N	Nor	Neg	Nor	No	No	Pos	Pos
59	31	F	L	Positive	Absent	Absent	Absent	No	N	N	N	Nor	N	No	No	No	No	No	N	Nor	Pos	Nor	No	No	Neg	Neg
60	55	F	D	Negative	Absent	Absent	Absent	No	N	N	N	Abn	N	No	No	No	No	No	N	Nor	Neg	Nor	No	No	Neg	Pos
61	43	F	D	Positive	Absent	Absent	Absent	No	N	N	N	Abn	N	Yes	Yes	Yes	No	Yes	SR	Pos	Pos	ILD	No	No	Pos	Pos
62	42	F	D	Negative	Absent	Absent	Absent	No	N	N	N	Abn	Mod. PHT	Yes	Yes	No	No	No	SR	Pos	Pos	ILD	No	Yes	Neg	Pos
63	18	F	L	Positive	Absent	Absent	Absent	No	N	N	N	Nor	N	No	No	No	No	No	N	Nor	Neg	Nor	No	No	Neg	Pos

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Figure 7 : SPHT