Cutaneous profile and nail fold dermoscopy in patients with scleroderma

DISSERTATION SUBMITTED IN THE PARTIAL FULFILMENT OF THE REQUIREMENTS OF TAMIL NADU DR.M.G.R. MEDICAL UNIVERSITY FOR THE DEGREE OF M.D. BRANCH XX (DERMATOLOGY, LEPROSY AND VENEREOLOGY) EXAMINATION TO BE HELD IN APRIL 2016

CERTIFICATE

This is to certify that the dissertation entitled "**Cutaneous profile and nail fold dermoscopy in patients with scleroderma**" is a bonafide original work done by Dr.Priya Sara Kuryan.

This study was undertaken at the Christian Medical College and Hospital, Vellore from February 2014 to September 2015, under my direct guidance and supervision, in partial fulfillment of the requirement for the award of the MD degree in Dermatology, Venereology and Leprosy of the Tamil Nadu Dr.M.G.R Medical University.

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DECLARATION

I hereby declare that this M.D. dissertation entitled **"Cutaneous profile and nailfold dermoscopy in patients with scleroderma**"is the bonafide work done by me under the guidance of Dr. Dincy Peter, Professor, Department of Dermatology, Venereology and Leprosy, Christian Medical College, Vellore. This work has not been submitted to any other university in part or full.

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Acknowledgements

First and foremost I would like to express my heartfelt sincere gratitude to my guide Dr. Dincy Peter for her immense support, guidance and encouragement throughout this study.

I would like to thank my co-guides Dr. Susanne Pulimood and Dr John Mathew for their immense help and guidance in completing this dissertation.

I also express my gratitude to my co-guide Dr. Leni George for her guidance and help in recruitment of patients.

I would also thank Dr Renu George for her guidance throughout this dissertation

I would like to thank my co-investigator Mr. Jayakanthan for his assistance in assessing serum IL-6 levels.

I would like to thank the Department of Rheumatology, especially the Professors and Registrars for helping me with recruitment of patients.

I would like to thank Dr. Nirmal, Dr. Anu Anna George, Dr. Lydia Mathew, Dr. Anjana Joseph, Dr. Gauri and Dr. Shanthi for their valuable inputs and help in recruitment of patients.

I would like to thank my colleagues for their constant support and help in recruitment of patients.

I thank Mrs. Linda for her secretarial assistance for the completion of the study and Mr. Lazarus Raj Premkumar for his help in photography.

A special thanks to my family, especially my father and sister without whose support this dissertation would have been impossible.

I would like to thank all the patients who were willing to take part in the study.

Last but not the least I would like to thank God Almighty for giving me courage and the strength for helping through this dissertation.

ABBREVIATIONS

ACR	American College of Rheumatology
ANA	Antinuclear antibody
ACA	Anticentromere antibody
ACEI	Angiotensin converting enzyme inhibitor
Anti Scl-70	Anti -topoisomerase
BANK	B-cell Scaffold Protein with Ankyrin Repeat
CENP	Centromere proteins
CMV	Cytomegalovirus
CREST	Calcinosis, Raynaud's phenomenon, oesophageal Dysmotility, Sclerodactyly, Telangiectasia
CRP	C- reactive protein
CT	Computer Tomography
CTGF	Connective tissue growth factor
CXCL4	CXC chemokine ligand 4
DLCO	Diffusing capacity of the lung for carbon monoxide
ECG	Echocardiogram
ESR	Erythrocyte Sedimentation Rate
ET-1	Endothelin -1
EULAR	European League Against Rheumatism
HLA	Human Leukocyte Antigen

HPV	Human Papilloma virus
ICAM	Intercellular adhesion molecule
IL	Interleukin
IRF-5	Interferon Regulatory Factor 5
MCP	Monocyte Chemoattractant Protein
MMP	Matrix Metalloproteinases
MRSS	Modified Rodnan skin score
PDGF	Platelet Derived Growth factor
PTPN22	Protein Tyrosine Phosphatase Non Receptor type 22
RNAP	Ribonucleic Acid Polymerase
STAT	Signal Transducer and Activator of Transcription
TIMP	Tissue inhibitors of metalloproteinases
TGF	Transforming Growth Factor
Th-2	Type 2 T helper
U1RNP	U1 Ribonucleoprotein
VCAM	Vascular cell adhesion molecule
VEGF	Vascular Endothelial Growth Factor

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DEPARTMENT: Dermatology, Venereology and Leprosy

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Objectives: The primary objective was to describe the cutaneous manifestations and nailfold dermoscopy in Scleroderma. The secondary objective was to study interleukin 6 levels in subset of diffuse systemic sclerosis patients.

Methodology: We recruited 35 patients between a study period of February 2014 to September 2015. All patients were examined for cutaneous manifestation of systemic sclerosis and dermoscopy of the nail fold capillary was performed using Heine delta 20 dermoscope. The severity of the disease was assessed using a Modified Rodnan Skin score. In a subset of patients with diffuse systemic sclerosis interleukin -6 levels were assessed. The prelevence was expressed in term of percentage along with 95%

confidence interval. The association of dermoscopic capillary pattern and Rodnan skin score with various clinical manifestations was evaluated using χ^2 tests.

Results: In our study we had a female preponderance with 91% of patients with diffuse type of disease. Cutaneous sclerosis was present in 97.1 % of our patients with upper limb being the commonest site of involvement. Pigmanetary disturbances were commoner in our study (94.3%) with commonest abnormality being salt and pepper pigmentation. Commonent systemic manifestation was interstitial lung disease (74.3%). The commonest pattern in nalifold dermoscopy was dilated capillaries (91.4%). Scleroderma pattern was seen in 77.1% of our patients. Interleukin 6 was elevated in 2 of 7 of our patents.

INTRODUCTION

Scleroderma is an autoimmune condition of unknown aetiology which can affect the skin, blood vessels and internal organs. It was initially described in 1754 in a young Italian woman who presented with progressive thickening of the skin.(1) The skin involvement is a cardinal feature for the diagnosis of scleroderma. Other internal organs which can be involved include the lungs, gastrointestinal system, heart and the kidneys.

Scleroderma is classified into diffuse and limited type of disease based on the extent of skin involvement. The skin involvement in systemic sclerosis can be varied. Apart from the cutaneous sclerosis, the other skin manifestations include Raynaud's phenomenon, digital ulcers, gangrene, flexion contractures and telangiectasias. There are various diagnostic criteria for the diagnosis of scleroderma, the commonly followed one being the American College of Rheumatology (ACR) criteria. The diffuse type of disease is associated with increased internal organ involvement and worse prognosis. Scleroderma accounts for the highest proportion of mortality among patients with connective tissue diseases. The main causes of death in scleroderma include scleroderma renal crisis, pulmonary artery hypertension and pulmonary fibrosis. Hence early diagnosis and initiation of therapy is of utmost importance in improving the survival rates.(2)

Nail fold dermoscopy is a noninvasive technique which aids in the diagnosis of scleroderma. Presence of abnormal nail fold capillaries has been given a score of 2 in

the latest ACR- EULAR (American College of Rheumatology – European League against Rheumatism) criteria in the diagnosis of scleroderma. Nail fold dermoscopy helps in predicting the stage and extent of microvascular damage and also to differentiate primary Raynaud's phenomenon from Raynaud's phenomenon secondary to scleroderma and other related disorders. It also aids in the diagnosis of early scleroderma prior to the onset of skin symptoms.(3)

There have been no published Indian studies on the pattern of nail fold dermoscopy in scleroderma. Hence we conducted this study to look at the cutaneous profile and nail fold dermoscopy in patients with systemic sclerosis.

AIMS AND OBJECTIVES

Primary Objective

- To describe the cutaneous manifestations among scleroderma patients
- To study the nail fold dermoscopy findings and its correlation with systemic manifestation in scleroderma patients

Secondary objective

To study the levels of interleukin-6 among a subset of patients with diffuse systemic sclerosis

REVIEW OF LITERATURE

INTRODUCTION

Scleroderma is an autoimmune connective tissue disease of unknown aetiology which affects the skin, internal organs and blood vessels.(1) It is also referred to as progressive systemic sclerosis, systemic sclerosis and acrosclerosis.(4) Skin is the most commonly affected organ and cutaneous sclerosis is one of the cardinal feature for the diagnosis of scleroderma.(2) It affects three major pathogenetic hallmarks which include immune dysfunction, extensive skin fibrosis and vasculopathy. The interaction between these hallmarks is still unknown. Scleroderma is a heterogeneous disease with clinical features which vary from only cutaneous involvement to extensive internal organ involvement.

HISTORY

The first case was described in 1754 in an Italian lady who had progressive thickening of skin. Goetz postulated that scleroderma was a systemic disease and coined the term progressive systemic sclerosis.(4)

EPIDEMIOLOGY

Overall prevalence of the disease is estimated to be 4 to 489 cases per million individuals and incidence is 0.6 to 122 cases per million individuals.(5)(6) The prevalence in USA is estimated to be 240 per 1 million adults. The prevalence is lower in Britain and Japan and is about 35 cases per 1 million persons.(6) There are no standardised Indian studies on prevalence of the disease. The reported prevalence

based on a study in north India by Minz et al. is 120 cases per million of which Raynaud's disease was present in 50 cases per million and 70 cases per million had overlap disease. This study was a hospital based study on patients with ANA positive connective tissue disorders. The limitation of the study was that there were no well defined diagnostic criteria and the study was limited to north India.(7) Females were more affected than males with ratios varying from 3:1 to 14:1.(2) The reported male to female ratio in a previous Indian study by Sharma et al. was 1:5.2.(8) The male to female ratio in Iceland and Japan was higher than the Indian study and was 1:8 and 1:16 respectively. The male to female ratio in Australia was 1:4.(8)(9)(10)(11) The mean age of onset was 30 to 50 years with males having an earlier onset of the disease.(2)

The racial factor influences both the disease type and susceptibility. Europeans, white Americans and Australians more frequently have limited disease whereas diffuse disease is more commonly seen in black American and some Asian populations.(5) In a study by Pradhan et al. the prevalence of diffuse disease was 40.9% and limited disease was 29.1%.(12) Autoantibodies expression is also influenced by genetic factors.(5) (13)(14) Laing et al. reported that anti-centromere antibodies were commoner in white women (38%) compared to black women(17%) whereas anti scl-70 had similar prevalence in both groups(18.4 vs. 18.6%).(13) McNeilage et al. reported high prevalence of anti scl-70(76%) in non white Thais as compared to anticentromere(ACA) antibodies(4%).(14)

Systemic sclerosis has the highest case specific mortality among all the connective tissue disorder and is influenced by race and ethnicity, age, extracutaneous involvement and disease subtype.(2)

The commonest cause of mortality is progressive pulmonary fibrosis; other causes include pulmonary artery hypertension, severe gastrointestinal involvement and renal crisis. Renal crisis accounts for early mortality in systemic sclerosis.(6) The survival rate is dependent on the internal organ involvement and has improved over the past years due to introduction of new drugs. The estimated 10 year survival rate is 70 to 80%.(6)(15)

PATHOGENESIS

The pathogenesis of scleroderma is not clearly understood and is said to be an autoimmune disease involving the cellular and humoral immune system.(2)(1)(16) The key pathogenetic changes are immune dysregulation with formation of auto antibodies, vascular changes and fibrosis which is characterised by deposition of collagen in the extracellular matrix.(1) The clinical heterogeneity is influenced by the predominant pathogenetic mechanism in the affected patients.(2)

AETIOLOGY

The exact aetiology is not known and the factors include genetic, infectious and environmental factors.(2) The diagrammatic representation of aetiology of scleroderma is depicted in figure -1.

Genetic factors

A positive family history contributes to 13 fold risk for acquisition of disease.(2) Assasi et al. showed that families affected by scleroderma showed concordant auto antibodies.(17) Monozygotic twins and dizygotic twins showed 90% and 40% concordant auto antibodies respectively. Shared genes is gaining prominence in the pathogenesis of scleroderma. Multiple genes in immune regulation which play a role in pathogenesis of scleroderma include BANK1, IL-23R, IRF-5 and PTPN22.(18) Studies have suggested an association of antifibrillarin positive patients with HLA-DR1*1302, DQB1*0604/0605 halotype. Anti Pm-scl antibodies are associated with HLA SRB1*03. STAT 4 gene is associated with both diffuse and limited disease.(19) BANK-1 and IRF -5 alleles showed 1.43 increased risks for diffuse type of disease. (20)

Infectious factors

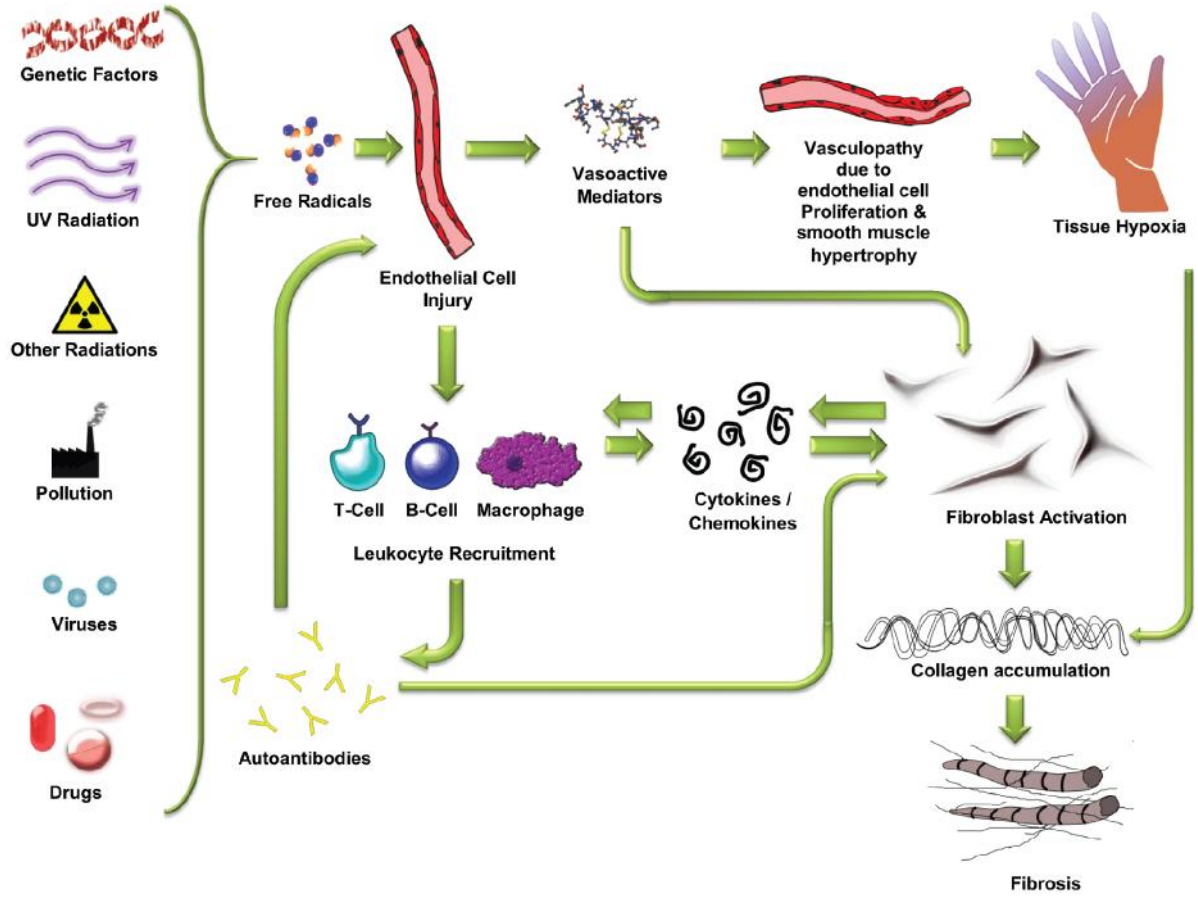
Infections with Parvo virus B19, Human Papilloma Virus, Cytomegalovirus (CMV) and toxoplasmosis is said to have a role as elevated antibodies have been detected in a few patients. It is attributed to possible molecular mimicry with autoimmune response induction. (21)(20)

Environmental factors

Occupational exposure to chemicals like silica, vinyl chloride, trichloroethylene, benzene carbon tetrachloride and epoxy resins have been implicated to cause scleroderma.(22)(23)(24)(25)(26) Drugs causing scleroderma like disease include bleomycin, cocaine and pentazocine. Radiation therapy can also be a contributing

factor. Smoking is an important factor which plays an important factor in induction and maintenance mechanism of vascular changes.(20) Hypovitaminosis D was associated inversely with skin severity, decreased DLCO levels and high pulmonary artery pressure.(27)(28)

FIGURE -1: AETIOLOGY OF SCLERODERMA (20)



Vascular Dysregulation

Vascular dysregulation is an early change in the pathogenesis of scleroderma preceding fibrosis.(1)(29) The blood vessels affected range from the small capillaries

in the proximal nail fold to the pulmonary arteries.(1) The primary event is vascular injury and activation of vasoactive mediators. Initial vascular injury is characterised by endothelial injury which is mediated by various factors which include environmental stress, proteolytic enzymes, cytokines, viruses and endothelial directed auto antibodies.(20) The earliest sign is vasodilatation – vasoconstriction imbalance leading to increased vascular permeability. Vasodilatation is mediated by nitric oxide, calcitonin related gene peptide and prostacyclin. Vasoconstriction is mediated by endothelin 1(ET-1), alpha-2 receptors and angiotensin II. Impaired vasodilatation- vasoconstriction balance leads to impaired blood flow and tissue hypoxia.(20)(2)

The endothelial activation causes expression of the cell adhesion molecules which causes transendothelial migration and perivascular accumulation of both T and B lymphocytes and macrophages. The inflammatory cells produce cytokines and transforming growth factor beta (TGF-ß) along with endothelin factor-1 which leads to an activation of myofibroblasts which leads to subendothelial fibrotic tissue along with platelet aggregation and intravascular thrombosis. These changes lead to microvascular occlusion. In scleroderma, there is impaired neoangiogenesis which is mediated by vascular endothelial growth factor (VEGF) and its receptor along with TGF-ß. Transforming growth factor beta (TGF-ß) leads to accumulation of collagen in extracellular matrix. Anti endothelial antibodies also contribute to endothelial apoptosis. Elevated levels of von Willebrand factor, fibrinogen and plasma proteins

also contribute to micro-occlusion. Digital ulcers and Raynaud's phenomenon is attributed to reversible vasospasm along with arterial damage whereas renal crisis and pulmonary artery hypertension are attributed to large vessel dysregulation. (4)(20)(2)

Endothelin-1 is a strong vasoconstrictor which also has fibrotic properties. It activates fibroblast collagen production along with leukocyte adhesion molecule activation. It has two receptors ET-A and ET-B of which ET-B is down regulated causing vasoconstriction and fibrosis. Elevated levels of ET-1 are seen in patients with minimal fibrosis with associated pulmonary hypertension and primary vascular disease and in patient with the diffuse type of disease. Elevated ET-1 also correlates with the severity of Raynaud's phenomenon, digital ulcers, pulmonary hypertension and renal crisis.(20)(30)(31)(32)(33)

Immune dysfunction

Immune dysfunction appears to play a role in the pathogenesis of systemic sclerosis and affects both the humoral and cell mediated immunity.(1) The initial inflammatory cells include T cells, B cells, mast cells and macrophages. In the later stages the T lymphocytes are the predominant cells which lead to oligoclonal expansion with a predominant Th2 response. This is demonstrated by elevated levels of Th-2 related cytokines in scleroderma patients which include interleukins 2, 4, 10, 13 and 17.

Toll like receptors and non toll like receptor activation lead to the activation of B cells which in turn activates interleukin 1 and 6 along with TGF-ß. These cytokines lead to accumulation of collagen in the extracellular matrix which eventually leads to fibrosis.(20)(2)

Evidence shows that interleukin 6 may be critical in the pathogenesis of systemic sclerosis. Interleukin-6 (IL-6) is a pro-inflammatory cytokine which is an acute phase protein and hence is elevated in the early stage of the disease. Interleukin 6 levels are elevated in diffuse and limited type of disease. Polymorphisms in the IL-6 gene may lead to an increase in susceptibility to develop systemic sclerosis. IL-6 and fibrotic events may be mediated directly through transcriptional activation of collagen. It may be mediated indirectly through the upregulation of other cytokines acting in an autocrine manner. Addition of IL-6 to fibroblasts in the dermis leads to upregulation of collagen which eventually leads to fibrosis. It is still unclear at a molecular level how elevated IL-6 contributes to fibrosis. Elevated levels of IL-6 were also proportionate to skin thickness suggesting a possible causal relationship.(34) Elevated IL-6 levels also correlated with antihistone antibody levels and levels decreased with treatment.(35) Interleukin 6 also has a protective role in the gut mucosa and use of IL-6 antagonists was associated with exacerbation of gastrointestinal symptoms.(36) Increased IL-6 levels were also associated with avascular areas in dermoscopy which was associated with higher incidence of the digital ulcers.(37) Increased IL-6 levels are also associated with increased CRP levels which correlated with disease severity, decreased

survival and worse outcome.(38) Studies are underway in developing anti IL-6 antibodies as a possible therapeutic target.(39)

Auto-antibodies production

Majority(95%) of patients with scleroderma have positive auto antibodies which have diagnostic and prognostic implications.(2)(28) Table 1 demonstrates the various auto-antibodies associated with scleroderma and its clinical association.

TABLE 1: AUTO-ANTIBODIES IN SCLERODERMA(2)

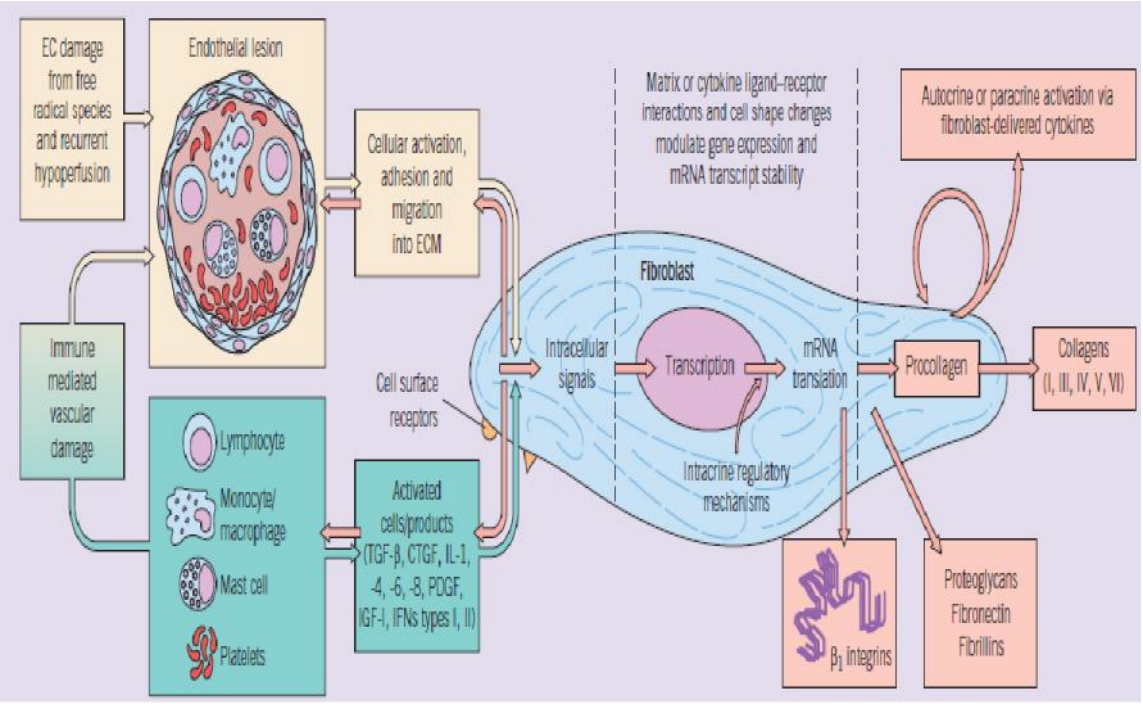
AUTOANTIBODY	CLINICAL ASSOCIATION
Scl -70	Diffuse type of disease Pulmonary fibrosis secondary pulmonary artery hypertension
Anti centromere	Limited type Isolated pulmonary artery hypertension Calcinosis Severe GI involvement
U1RNP	Overlap features Arthritis
RNAP-III	Diffuse type Renal crisis
Pm-scl	Limited type Myositis overlap Calcinosis
Fibrillarin	Diffuse type Pulmonary artery hypertension Renal disease Myositis
Th/To	Limited type Pulmonary fibrosis

Fibrosis

Fibrosis is the final pathogenetic mechanism in the development of scleroderma leading to collagen deposition in the extracellular matrix of the skin as well as internal organs. The main contributor is the fibrogenetic fibroblasts. The factors contributing to inappropriate activation along with growth enhancers and down regulators are still not clearly understood. There is up regulation of collagen types I, III, V, VI, VII and XIV. This is mediated by cytokines like TGF-ß. Transforming growth factor -ß is mitogenetic for fibroblasts and leads to accumulation of collagen, glycosamineglycans and fibronectin. There is also increased expression of proteases like thrombin and tryptase which leads to synthesis of matrix. There is down regulation of matrix metalloproteinases (MMP) like MMP 3,7and 12 with elevation of tissue inhibitors of metalloproteinases (TIMP) and presence of anti MMP auto antibodies. Transforming growth factor -ß is also related to Connective Tissue Growth Factor (CTGF) which is a strong inducer of collagen production and is important in maintenance of extracellular matrix. Fibrillin-1 is seen in the dermis and fibrillin-2 is seen in the vascular tissue and basement membrane. Autoantibodies are present against short fragment of fibrillin -1 which help in remodeling during fibrosis. Antibodies against fibrillin-2 are associated with wnt pathway and TGF-ß.(40) Wnt pathway is associated with pulmonary fibrosis.(41) In a study by Wei et al on a mouse model, wnt 10b was associated with TGF-ß dependent dermal fibrosis and loss of adipose tissue.(42) Antibodies against platelet derived growth factors (PDGF) receptor activate gene expression of collagen

and eventually lead to fibrosis. Other factors which contribute to fibrosis include VEGF, ET-1, IL 13 and 21 and Monocyte chemoattractant Protein(MCP) protein. Some evidence suggests that there is an autocrine mechanism leading to hypersensitivity of growth factors in the scleroderma affected fibroblasts. Other evidence suggest that normal fibroblasts when exposed to an abnormal microenvironment leads to enhanced expression of growth factors which lead to collagen synthesis. (2)(20)(43) Proteome wide analysis showed that CXCL4 is the predominant protein secreted by plasmactytoid dendritic cells in scleroderma.(46) CXCL4 can serve as a biomarkers for skin fibrosis and pulmonary fibrosis and also predict the progression in patient with scleroderma phenotypes.(38) The interaction between endothelial cells, fibroblasts and leucocytes are demonstrated in figure -2.

FIGURE 2: PATHOGENESIS



CLASSIFICATION

Systemic sclerosis was classified by Leroy in 1988 based on the extent of skin involvement as shown in figure 3.(44)

The limited type is characterized by involvement of the distal extremities and the face. The ADF (Arbeitsgruppe Dermatologische Forschung) classification is used in limited acral disease, type 1 is defined as involvement up to ankle joint and hand and type 2 is defined as involvement of more proximal limbs and face.(44) Barnett et al. classified skin sclerosis as type I including sclerodactyly, type 2 as proximal to metacarpophalangeal joint with no involvement of the trunk and type 3 includes involvement of the trunk.(45) Limited disease is characterised by late organ involvement and anti CENP antibodies positivity (50 to 90%) of patients. A certain subset of patients with limited type of systemic sclerosis have CREST syndrome (calcinosis, Raynaud's phenomenon, oesophageal involvement, sclerodactyly and telangiectasia). Diffuse type of systemic sclerosis is characterised by early organ involvement and anti Scl 70 positivity. Systemic sclerosis sine scleroderma refers to Raynaud's phenomenon with positive serology with no cutaneous involvement. (4)(44) The differences between diffuse and limited disease are shown in table-2.

FIGURE 3 – CLASSICATION

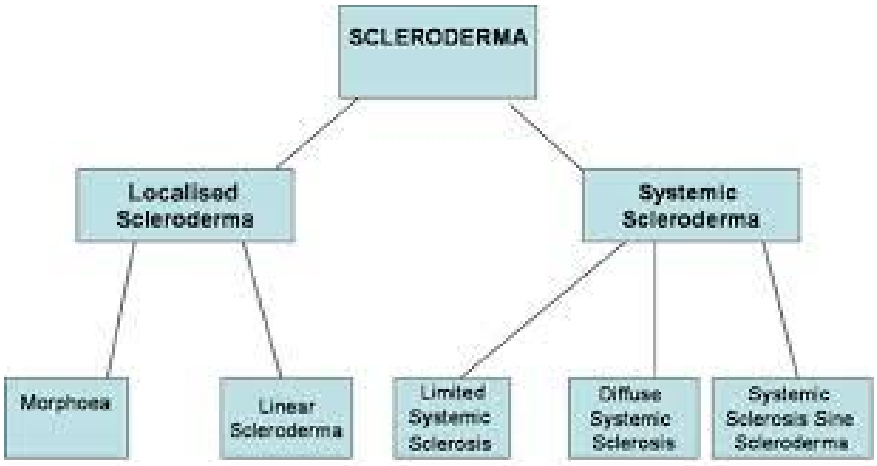


TABLE 2 : DIFFERENCES BETWEEN DIFFUSE AND LIMITED TYPE (2)

	DIFFUSE	LIMITED
Extent	Extremities, face, trunk	Extremities, face
Raynaud's phenomenon	Within 1 year	Many years to decades
Organ involvement	Early	Late
Tendon friction rub	Present	Absent
Antibodies	Anti topoisomerase -I(30 to 40%)	Anti CENP (50 to 90%)

Organ involvement is early in diffuse systemic sclerosis and there is early onset of pulmonary fibrosis. Pulmonary artery hypertension is common in the limited disease and has a late onset. Renal crisis is commoner in diffuse systemic sclerosis.

SCLERODERMA DIAGNOSTIC CRITERIA

The diagnosis for scleroderma is made on the basis of the criteria devised by American college of rheumatology (ACR) in 1980

Major criteria – symmetric proximal sclerosis extending beyond metacarpal phalangeal joint and metatarsal joint

Minor criteria – 1) sclerodactyly

2) digital pitted scars/loss of substance over finger pads

3) bibasilar fibrosis

The diagnosis is made on the basis of presence of one major or two or more minor criteria.

This criterion has a sensitivity of 97% and specificity of 98%. The limitation of this classification was that patient with early systemic sclerosis and 20% of patients with limited disease were excluded from diagnosis.(46)

Leroy and Medsger in 2001 modified the earlier ACR criteria to include early systemic sclerosis. Early scleroderma was diagnosed on the basis of abnormal capillary findings and presence of auto-antibodies in the absence of cutaneous features.(47)

Recently, a new classification criteria of systemic sclerosis has been recommended by the European League against Rheumatism (EULAR) and American College of

Rheumatology (ACR) which is shown in table 3. According to this criteria skin thickening of both hands extending proximal to the metacarpo-phalangeal joint is sufficient for diagnosis of scleroderma. In addition there are 7 items with subsets having weighted scores. The subset with higher score is taken for calculation of the total score. A score of $\geq$ 9 is required for diagnosis. This criterion has a sensitivity of 91% and specificity of 92%.(48)

TABLE 3: EULAR CLASSIFICATION

ITEM	SUBSET	POINTS
Skin thickening of both hands extending proximal to the mcp joint(sufficient criterion)		9
Skin thickening	Puffy fingers Sclerodactyly(distal to MCP joint and proximal to PIP joint)	2 4
Fingertip lesions	Digital tip ulcers Digital pitted scars	2 3
Telangiectasia		2
Abnormal nail fold capillaries		2
Lung involvement	Pulmonary artery hypertension Interstitial lung disease	2 2
Raynaud's phenomenon		3
SSc related auto antibodies	Anticentromere 3 Antitopoisomerase I Anti RNA polymerase III	3

CLINICAL FEATURES

The most commonly involved organ is the skin which is almost always affected and is considered to be the cardinal feature for diagnosis. The other organs involved are lungs, heart, kidneys, gastrointestinal system and heart.(2)

Cutaneous Features

The most commonly involved sites include the hands, face and the lips. In a study done in Leeds, hands were involved in 95% followed by the chest in 30% and feet in 15%.(4)

Skin sclerosis

The skin over the hands and face are the most commonly involved sites. The stages in skin involvement include oedematous, indurated and atrophic phases. In the oedematous phase, there is pitting edema involving the digits with a doughy feel also called sausage digits. The oedema is attributed due to deposition of dermal glycosaminoglycan, vascular and hydrostatic changes.(1) It progresses to the indurated phase or the sclerotic phase where the skin becomes taut and shiny. Rapid progression from indurated phase to sclerotic phase is associated with bad prognosis and diffuse involvement. The fingers at this stage are referred to as Madonna's fingers.(49) The cutaneous sclerosis typically starts acrally involving the finger tips and hands but may progress proximally and symmetrically to involve the trunk and

face. There is associated decreased sweating, loss of hair with loss of skin creases with inability of skin to fold. It progresses to the final stage, the atrophic stage where the skin becomes tight and hidebound with loss of subcutaneous tissue and formation of flexion contractures and digital ulcers. Rapid progression of sclerosis is associated with bad prognosis whereas gradual progress is associated with a good prognosis. (49)(4) Skin sclerosis was seen in all patients in a study by Krishnamurthy et al. and in 98.5% of patients in a study by Sharma et al. The prevalence of skin sclerosis was 86% in the whites and 96% in African American in a study by Reville et al. (8) (50) (53)

Face involvement

In a well developed case there are characteristic facial features. The skin is bound down and hard with shiny forehead and loss of expression lines with typical mask like facies. The nose is small with pinched or beaked appearance. The mouth opening is decreased with pursed appearance due to radial furrows and thinning of upper lips. Microstomia can be associated with difficulty in talking and eating. Inter-incisor distance can be decreased in both the vertical and horizontal direction in scleroderma.(4) The lower eyelid cannot be everted due to loss of subcutaneous tissue(Ingram's sign).(51) Mucosal involvement can present with frenulum shortening secondary to sclerosis.(52) Rarely, periorbital oedema and mandibular atrophy have been reported. (53) Chondrodermatitis nodularis helicis was reported in

3 of 21 patients with limited disease. They present as painful nodules over the helix of the ear.(54)

Neck sign

The neck sign also referred to as Barnett's sign is the prominence of the platysma on hyperextension of the neck and seen in 90% of the patients. It is a useful diagnostic tool to differentiate from primary Raynaud's phenomenon and in case of limited or early scleroderma where clinical features may not be apparent.(55)(56)

Pigmentary disturbances

Pigmentary disturbances are present in 50% of the patients and can present as salt and pepper pigmentation, depigmentation and diffuse hyperpigmentation. Patients presenting with diffuse hyperpigmentation have accentuation in sun exposed areas and pressure areas. Salt and pepper pigmentation also referred to as leucoderma of scleroderma presents as depigmentation with retention of perifollicular pigmentation. It commonly involves the upper trunk and face, but may also involve uninvolved skin and sclerotic skin.(1)(4)(52) In a study by Sharma et al. the pigmentary abnormalities noted were diffuse pigmentation in 88.1%, mottled hypo-depigmentation (salt and pepper-like pigmentation) in 51.2% and depigmentation at the sites of scars in 31.3%.(8)

The mechanism of pigmentation in scleroderma is not known. Endothelin -1(ET-1) which is produced in the keratinocytes promotes melanin synthesis and melanocyte production. Increased ET-1 production in keratinocytes has been correlated with

pigmentation and can be associated with severe disease.(57) The retained perifollicular pigmentation is attributed to retainment of melanogenesis in the perifollicular capillaries.(58)

Telangiectasias

Mat like telangiectasias is present in 75% of the patients and varies in size from 2mm to 20mm. It is commonly seen in face, mouth, lips, hands and upper trunk. They are representative of dilated venules and blanch on pressure. It can be present in the limited and diffuse type of disease.(4)(52) In a study by Sharma et al. the prevalence was 36.8%, the prevalence in the western population was 51% in the whites and 59% in the Hispanics.(8)(59)

Calcinosis cutis

Calcinosis cutis is a type of dystrophic calcification which presents as discharging chalky white discharge over the fingers, hand, elbow, knee, ankle and the iliac crest. It generally presents late in the disease course. Calcinosis cutis is seen in 25% of the patients and more commonly affects the females.(4)(52)(60)

Digital ulcers

The ulcers commonly involve the finger tips, but may also involve the ulnar border of the thumb and radial border of index finger. The digital ulcers may progress to form gangrene or undergo auto amputation or may resolve with scarring. The scars are normally present over the finger tip but may also involve the ulnar border of the

thumb and radial border of index finger.(4)(61) In a study by Sharma et al., the prevalence of digital ulcers was 58.6% and in a study by Krishnamurthy et al. the prevalence was 47.4%. The prevalence in the western population was higher (82%) as studied by Reville et al.(59)

Round finger pad sign

This sign refers to replacement of finger tip contour from peaked to hemisphere like tip. It is most commonly seen in the ring finger. It can serve as a clinical tool for early diagnosis of scleroderma. It can also be present in mixed connective tissue disorder and primary Raynaud's disease.(62)(63)

Nail changes

The nails curve over the atrophic phalanges and become small with atrophy of distal portion of the fingers. Other nail changes include ragged cuticle, paronychia, beaking of nails and pterygium inversum unguis. Pterygium inversum unguis is not specific to scleroderma and can be present in other connective tissue diseases. (4)(64)(65)(66)

Lower limb involvement

In the lower limbs the skin manifestation of scleroderma could be ulcers (40%), livedo reticularis or atrophie blanche.

Other rare cutaneous findings include hyperkeratotic plaques over the phalanges due to deposition of amyloid, small papules secondary to lymphangiectasia and lesions

resembling acrokeratoelastodosis.(67)(68) Rarely, they can be present as subcutaneous nodules resembling erythema nodosum.(69)(70)

Raynaud's phenomenon

Scleroderma is one of the commonest causes of secondary Raynaud's phenomenon. It is characterised by white, blue and red discoloration of fingers due to episodic vasospasm of the digital arteries due to cold stimuli. At least two phases are required for the diagnosis of Raynaud's phenomenon. It is seen in 90% of patient with diffuse systemic sclerosis and 99% with limited systemic sclerosis.(49)(71) The prevalence of Raynaud's phenomenon was 92.9%, 100% and 96% in studies by Sharma et al., Adhadh et al and Reville et al respectively. (8)(72)(59) Other causes of Raynaud's phenomenon include connective tissue disorders like Sjogren's disease and SLE, carpal tunnel syndrome, secondary to drugs like bleomycin, frost bite and exposure to vinyl chloride.(1) Raynaud's phenomenon represents an imbalance in the vasodilatation –vasoconstriction cycle favoring vasoconstriction.(73)

ASSESSMENT OF SKIN INVOLVEMENT

1. *Rodnan skin scores*

   It is a semi-quantitative tool which measured 26 sites and weighed the skin biopsies and collagen content. The modifications include 17, 20 and 22 sites. (Annexure - III). It is an easy bed side test to assess disease severity and also is of prognostic value. Increased score is associated with internal organ involvement. The disadvantage is that it has high intra and inter observer

variability and does not differentiate between thickening and tightness. (74)(75)

2. *Durometer*

   It is used to measure the hardness of the skin. Its values correlate with values of Modified Rodnan Skin Score(MRSS) and ultrasound.(75)(76)(77)

3. *Ultrasound*

   Ten to 30 hertz ultrasound are useful in assessment of skin thickness. Dermal thickness is more accurately measured with 20 to 30 hertz. It produces good results with minimal intra and inter-observer variability. The disadvantage is the time constraints.(75)(77)

4. *Plicometer*

   It measures the thickness of folded skin (plica) but is yet to be validated. It is more sensitive and specific than mRSS and can be used for follow up of patients.

5. *Magnetic Resonance Imaging - skin*

It measures skin thickness with musculoskeletal involvement along with calcinosis. The disadvantage is that it is expensive.

6. *Skin biopsy*

   The degree of sclerosis can be assessed by measuring the collagen content and the dermal thickness. Hydroxyproline content can also be correlated with skin scores.

7. *Others*

Twistometer, cutometer, elastometer(77)

Extracutaneous involvement

Respiratory system

Respiratory involvement is the leading cause of death in patients with systemic sclerosis. It may manifest as pulmonary artery hypertension or interstitial lung disease. Pulmonary artery hypertension though present in both types, is more typical for the limited type. It is of prognostic significance and early initiation of therapy improves survival.(4) In a study by Sharma et al., the prevalence was 51% and in a study by Pradhan et al. it was 77.3%.(8)(12) In a study conducted in Thailand by Ruangjutipopan et al. and in Iraq by Adhadh et al. the prevalence was 57.4% and 32% respectively.(78)(72)

Renal system

Renal involvement is the commonest cause of acute mortality and has one of the worst prognosis among the internal organ involvement. Acute renal crisis is the greatest risk in patients with rapidly progressing diffuse type of systemic sclerosis and they present with malignant arterial hypertension, cramps, visual disturbances and left ventricular hypertrophy. These patients benefit from early initiation of Angiotensin Converting Enzyme inhibitors(ACEI) and regular monitoring of blood pressure.(4)(52) The prevalence of renal involvement was 6% and 10.9% in two studies from India.(8)(12) A study in Thailand by Ruangjutipopan et al. and Iraq by

Adhadh et al. showed renal involvement in 5.8% and 9% of their study population.(78)(72)

Cardiovascular involvement

Cardiovascular involvement can present with pericardial or myocardial involvement and conduction abnormalities. It can also be secondary to the kidney and lung involvement. Pericardial effusion is generally asymptomatic. Conduction abnormalities are complete heart block, atrial tachycardia, atrial fibrillation and ventricular tachycardia. The most serious complication is myocardiopathy which presents with cardiac fibrosis and rapidly progressive myocardial failure.(4) In a study by Pradhan et al, the cardiovascular involvement was seen in 13.6% of patients. (12)

Gastrointestinal involvement

Gastrointestinal system is a common internal organ involvement. It presents with gatroesophageal reflux and distal dysphagia. Chronic oesophagitis may be associated with ulceration and stricture formation. The involvement of the stomach may result in delayed peristalsis with dilatation and delayed gastric emptying. Gastric antral vascular ectasia is seen in the diffuse type of systemic sclerosis and is referred to as watermelon stomach due to its endoscopic appearance. The duodenum involvement results in postprandial bloating, abdominal pain and regurgitation. The intestinal involvement presents with recurrent pseudo obstruction or malabsorption. Rarely, mega colon, rectal prolapse or colonic diverticula may be present. Primary biliary

cirrhosis can also be associated.(1)(4) In a study by Sharma et al, the prevalence of GI involvement was 70.2% and in a study by Pradhan et al. it was 7.3%.(8)(12) The prevalence of GI involvement was 41.9% in studies from Thailand and Iraq.(78)(72)

Musculoskeletal involvement

Systemic sclerosis is the only condition where phalangeal absorption is associated with calcinosis. In 70% of the cases the phalangeal absorption is mild and affects only one terminal phalange. It can also involve the middle and proximal phalanges and develop erosive arthropathy involving the distal inter-phalangeal joint similar to psoriatic arthropathy. Resorption of the zygomatic arches and mandible can present with pain in the temporomandibular joint and grinding sensation on chewing. Osteolysis can also affect the shoulder joint, ribs, cervical spine, radius and ulnar bones. Rarer associations include intraosseous deposition of calcium, avascular necrosis of femoral head and osteopoikolosis which is characterized by islands of bone in the epiphysis and the metaphysis. In some cases carpal tunnel syndrome may be the presenting complaint. The involvement of juxta-articular tendons can lead to fibrosis and result in friction rub.

Myopathy can present in two ways, inflammatory and the non- inflammatory type. The non inflammatory type is commoner and present in 60 to 80% of the patients and presents with minimal elevation of CPK with mild weakness. The inflammatory type simulates polymyositis and is characterised by elevated CPK and aldolase levels and positivity for PM-Scl antibodies.(4)(52)

Dental involvement

Periodontal widening can be secondary to fibrosis and thickening of the vessel wall . Stafne's sign refers to widening of periodontal ligament space. It occurs in 30% of the patients and can affect the entire root, anterior and posterior teeth and lamina dura. It can also lead to osteolysis of the coronoid process and mandibular angle leading to loss of teeth.(52)

Neurological involvement

Neurological involvement is rare and affects less than 10% of the patients. It can present as trigeminal neuralgia which initially presents unilaterally which may progress to become bilateral. Other neurological manifestations include peripheral neuropathy, carpal tunnel syndrome, meralgia paraesthetica and spinal cord compression secondary to calcification. Sub acute combined degeneration of spinal cord can be secondary to vitamin B12 deficiency.(4)(52)

Eyes

Decreased tear secretion, keratoconjunctivitis sicca, tightness of eyelids with shallow fornices are specific eye changes. Vascular involvement can lead to retinopathy with central retinal vein involvement.(79)(80)

Others

Sjogren's syndrome can be seen in 15% of the patients. Impotence and hypothyroidism secondary to thyroid fibrosis have also been reported. It can also present with overlap features of other connective tissue disease.(4)

AUTOANTIBODIES ASSOCIATED WITH SYSTEMIC SCLEROSIS

The investigations are broadly divided as investigations to confirm diagnosis and assessment of systemic involvement. Auto antibodies testing are useful in confirming the diagnosis. Antinuclear antibody (ANA) positivity is present in 78% and 97% with rat liver and Hep-2 cells. The common patterns include speckled, homogenous and nuclelolar with nucleolar and discrete speckled being specific for systemic sclerosis. Antibodies to topoisomerase I (Scl-70) causes diffuse frost staining of nuclei is seen in 20% of the patients and is associated with diffuse disease with increased risk for interstitial lung disease.(81) Anticentromere antibodies are associated with the limited type. Anti RNP antibodies is associated with risk of diffuse type of disease and renal involvement. Anti Sm antibodies are also associated with renal involvement. Other autoantibodies which are associated include antifibrillarin antibodies(associated with diffuse type), anti PM-Scl(associated with dermatomyositis overlap) and anti SSA (associated with sjogren's disease) as mentioned in table 2.

DIAGNOSTIC TESTS

Other serological abnormalities include anemia, elevated ESR (approximately 50%) and false positive VDRL in 5% of patients. There can be associated cold agglutinin positivity and cryoglobulinemia. Rheumatoid Factor is positive in 30% of the patients. The investigations which are done to evaluate systemic involvement include chest X-ray, electrocardiogram (ECG), echocardiogram, barium swallow and renal

function tests. Skin biopsy shows fibrosis of the lower dermis and subcutaneous tissue with sparse adnexa with perivascular sparse lymphocytic infiltrate.(4)

In a study by Sharma et al ANA positivity was present in 89.1% with commonest subtype being speckled in 62.1%.(8) The prevalence of ANA positivity was 85.5% , scl-70 was 62.7% and anticentromere antibodies was 22.7% in the study by Pradhan et al.(12)

ASSESSMENT OF VASCULAR INVOLVEMENT

The clinical manifestations of vascular involvement of scleroderma are diverse and include Raynaud's phenomenon, digital ulcers and pulmonary arterial hypertension. (82). The changes involve the microcirculation as well as arterioles. The assessment of the vascular involvement include clinical parameters , non invasive techniques and detection of circulatory markers.(83)

CLINICAL PARAMETERS

1) *Raynaud's Phenomenon*

   The propensity of vasospasm is best demonstrated by Raynaud's phenomenon. Attacks of Raynaud's phenomenon are assessed by the involved digits, frequency, and symmetry, severity of symptoms and assessment of pain. Raynaud's Condition Score (RCS) combines visual analogue score with frequency and duration of attacks.

2) *Digital Ischemia*

Digital ischemia is assessed by finger tip ulcerations which resolve with scarring and gangrene involving the fingers. It is important to note the digital scars (active/ pitted), atrophy of digital pads and digital amputations.

3) *Telangiectasias*

Telangiectasias are dilated small blood vessels which are visible to the naked eye and are representative of dilated capillaries and venules. They are commonly seen in the limited type of disease.

NON INVASIVE TECHNIQUES

The non-invasive techniques for assessing vascular involvement include functional assessment, digital blood pressure, skin temperature, digital vascular response to endothelial dependent and independent dilators, nail fold capillary examination, transcutaneous oxygen pressure and exercise performance.

1) *Functional assessment*

Functional assessment includes Doppler studies and provocative tests. Doppler studies assesses blood flow in the vessels by measuring the velocity, waveform, wall lumen ratio and digital pressure. The flow patterns should be assessed in the digital radial arch, palmar and digital arteries. Studies have showed that there is a decrease in all parameters in primary and secondary Raynaud's phenomenon but it is difficult to differentiate between the two

types. Provocative tests include cold challenge and assessment of vasodilatory capacity.

(i) Cold challenge test

This test is performed by exposure of finger to cold or whole body cooling using a cooling blanket in a temperature controlled room. The circulatory adequacy is assessed by measurement of digital pressure, skin temperature and flow studies every 5 minutes till it returns to normal temperature. If it is prolonged for more than 20 minutes it is considered to be positive for Raynaud's phenomenon. This test does not distinguish primary from secondary Raynaud's phenomenon.

(ii) Assessment of vasodilatory capacity

Hyperemia is measured after heating the body up to 43°C and assessing flow using Doppler studies. In systemic sclerosis, maximum vasodilatation is inversely related to number of affected internal organs. (83)

(2) Digital Blood Pressure

Reduction in digital blood pressure by >70% after cooling helps in differentiating Raynaud's phenomenon secondary to systemic sclerosis from primary Raynaud's phenomenon and has 97% sensitivity and zero digital pressure at 30°C has 100% specificity.

(3) Skin Temperature

Skin temperature and digital pressure should be measured in a controlled environment. These parameters correlate inversely to digital ulcer healing time. (83)

CIRCULATING VASCULAR MARKERS

Vascular markers are cells that get detached from blood vessels which is indicative of vascular injury. It correlates with direct endothelial injury.The various markers which aid in the assessment of vascular involvement include:

(i) Soluble adhesion molecules: E –selectin, P-selectin, ICAM, VCAM - involve the involved and uninvolved skin. E and P selectin are associated with early disease and lung fibrosis. ICAM is associated with digital infarcts and VCAM is associated with elevated ESR and cardiac involvement.

(ii) Endothelin -1 levels

(iii) Nitric oxide

(iv) Prostacyclin

(v) Thrombomodulin

(vi) Anticentromere antibodies

(vii) Von willebrand factor

(viii) Antiendothelial cell antibodies

(ix) Angiotensin converting enzyme (ACE) levels

DERMOSCOPY

Dermoscopy helps in viewing morphological features which are not seen by the naked eye and serves as a link between morphological features and pathology.(84) In scleroderma its use is based on the principle that systemic vasculopathy affects the nail fold vascular configuration which leads to capillary loss, dilated and giant capillaries.(85)

History

It was first described in 1663 by Johan Christophorous when he described nail fold capillaries using a microscope. It was later described by the Italian Physician, Giovanni Rasori where he described a relationship between dilated capillary loops and conjunctival inflammation. Brown and O'Leary were the first people to describe the micro vascular abnormalities during Raynaud's phenomenon.(86)

Classification

Nail fold capillary changes are classified into normal pattern, scleroderma pattern and non specific type by Cutolo et al.(3)(87)

(a) Normal pattern - homogenous capillary distribution without capillary loss in the nail plexus (30 capillaries/5mm).

(b) Scleroderma pattern - divided into 3 types based on classification by Maricq et al and Bergman et al. It is said to be scleroderma pattern if it has two or more abnormalities.

i) Early pattern – The early pattern has relatively preserved capillary architecture with no obvious capillary loss and few enlarged or giant capillaries with few capillary hemorrhages.

ii) Active pattern –There is moderate capillary loss with frequent giant capillaries and capillary hemorrhages.

iii) Late pattern –There is severe capillary disorganisation with severe loss of capillaries with large avascular areas. There are frequent ramified or bushy capillaries.

Non specific type - The capillary changes don't have the complete scleroderma pattern

Nail fold capillaries were classified by the German study group (88)(89) as :

Stage I (ectasia) – normal capillaries with possible edema, capillary ectasia and bleeding

Stage II (individual megacapillaries) – ramification of capillaries, increasing oedema, increase in ectatic capillaries and mega capillaries

Stage III (predominantly megacaillaries) – decreased density, increased megacapillaries, increased oedema and deformity

Stage IV (scar) – severe oedema and avascular areas, few deformed capillaries

An absolute marker for scleroderma capillary pattern is giant capillaries with homogenous enlargement (diameter>50μm).(73) Giant capillaries are representative of abnormal angiogenic response to peripheral ischemia. Capillary haemorrhages are representative of Raynaud's phenomenon and multiple are more in favour of scleroderma. Avascular pattern is indicative of severe peripheral ischemia.(3)

Role of Dermoscopy in Systemic Sclerosis

1. It is useful in differentiating between primary and secondary Raynaud's phenomenon. Early detection of abnormal capillaries by dermoscopy maybe of significance with the advent of new drugs which affect vascular remodeling like ACEIs, endothelin receptor antagonists and prostanoids.(73)

2. It can also be used to predict the risk of developing systemic sclerosis based on capillary findings and Raynaud's phenomenon especially in the limited subtype of disease(68)

3. It is also useful as it may be the initial indicator of digital micro vascular injury and can be a useful tool for follow up.(87)(73)

4. Studies have shown vascular remodeling improves with addition of immunosuppressant, hence nail fold dermoscopy can be used as tool to assess response to treatment.(84)

Diagnosis of Early Scleroderma

Studies have shown that in children with Raynaud's phenomenon capillary changes occur 6 month prior to the onset of the disease suggesting a strong correlation between Raynaud's phenomenon and nail fold capillaries

Significance of various nail fold dermoscopic findings

1. Enlarged/giant capillaries –abnormal angiogenic response secondary to peripheral ischemia
2. Capillary haemorrhage – These are considered to be secondary to ischemia and reperfusion. Single haemorrhage can be present in normal individuals. Multiple haemorrhages are seen in scleroderma and dermatomyositis
3. Avascular areas – indicative of severe peripheral ischemia and increased probability of developing digital ulcers.
4. Bushy capillaries – These are present in hypovascular areas and are representative of abnormal angiogenic response (3)

D*ermoscopic patterns in other connective tissue disorders*

(a) Dermatomyositis – disorganised capillary architecture with bushy capillaries, less frequently capillary haemorrhages with giant capillaries may be seen

(b) Systemic lupus erythematosus - disorganised capillary architecture with dilated capillaries.

(c) Anti phospholipid syndrome – capillary microhaemorrhages are present

(d) Sjogren's syndrome – confluent capillary haemorrhages and pericapillary haemorrhages(86)

In a study done in Turkey showed that 83% of the scleroderma patients had nail fold capillary changes. The most common pattern was dilated capillary loops (47%) followed by giant capillaries(34%) and normal capillary configuration (17%). No difference was noted in capillary configuration in limited and diffuse systemic systemic sclerosis. Decreased number of capillary loops can also be predictive for extensive skin involvement and 49% had digital trophic lesions. (90)

Beltran et al. studied capillaroscopic features in 56 patients with Raynaud's phenomenon. Normal capillaroscopy was revealed in all patients with primary Raynaud's disease and 11 of 12 patients with pre scleroderma. Scleroderma pattern was observed in 73% of patients with limited disease and 82% of patients with diffuse disease. Avascular areas correlated with severe Raynaud's phenomenon, bone resorption and diffuse type of disease.(87)

A recent study by Hudson et al. also examined the reliability of dermoscopy in assessing nail fold capillary abnormalities. These investigators assessed inter- and intra-observer reliability in identifying the presence or absence of three specific features—dilated loops, giant capillary loops and avascular areas. Four fingers in each of six patients with systemic sclerosis and two controls were examined. For the

three features, the k-coefficients for inter-observer variability were 0.63 (dilated loops), 0.40 (giant capillaries) and 0.20 (avascularity), and for intra-observer variability 0.71, 0.55 and 0.40, the authors concluded that reliability for dilated and giant capillaries was good and that dermoscopy was therefore a useful tool.(91)

Ong et al. studied 20 patient with limited type of disease and concluded that patient with pulmonary artery hypertension had lower capillary density.(92) Hoftstee et al concluded that severity in pulmonary artery hypertension correlated with the nail fold density. The study did not find any correlation with other co-morbidities. (93)

Dermoscopy is a useful non invasive tool that differentiates between primary and secondary Raynaud's phenomenon. It is also useful in the early diagnosis as well as staging of the disease. It is a useful tool for prognostication and follow up. In conclusion it is a useful diagnostic tool and can serve as an indicator of internal organ involvement. (94)

MATERIALS AND METHODS

Study design

Hospital based cross-sectional study of all the patients with systemic sclerosis

Setting

The study was conducted in the Dermatology, Venereology and Leprosy Unit -2 OPD and the Rheumatology Out-patient Clinic and ward.

Study Duration

The study was conducted from February 2014 to September 2015(20 months)

Inclusion criteria

- Patient with diffuse systemic sclerosis who fulfill ACR criteria
- Patient with limited systemic sclerosis with sclerosis involving the hands and feet and are positive for anti-CENP antibodies
- Age > 16 years
- Patients who are willing to take part in the study

Exclusion criteria

- Patients with overlap with other connective tissue disorders
- Patients who do not wish to be included in the study

Inclusion criteria for measurement of interleukin 6 levels

- Patients with diffuse systemic sclerosis who fulfill ACR criteria and are positive for anti scl-70 antibodies
- Patients who are willing to take part in the study

Exclusion criteria for measurement of interleukin 6 levels

- Patient with limited systemic sclerosis
- Fever with active infection
- Associated malignancy

METHODOLOGY

Patients who fulfilled the inclusion criteria were enrolled in the study. The diagnosis of diffuse scleroderma were based on the American College of Rheumatology (ACR) criteria (Annexure -I) and the diagnosis of limited type was based on the presence of sclerodactyly and positivity for anti-CENP antibodies. All the patients and/or the guardians were informed about the purpose of the study and informed consent was obtained (Annexure –II).

All the patients were examined by the principal investigator and the details obtained from the patient or legal guardians were entered in a proforma (Annexure –III). The details were collected and subsequently entered in an electronic database.

Demographic details

Socio-demographic data including the age at recruitment into the study, gender, place of stay and duration of the disease were recorded.

History pertaining to the disease

1. Presenting cutaneous complaints(Raynaud's phenomenon, skin sclerosis) and duration of the same were recorded
2. Systemic complaints (gastrointestinal, respiratory, cardiac, renal, musculoskeletal) were recorded
3. Past history of skin lesions and treatment history including topical and systemic medications were recorded

Clinical examination

All patients were examined for the presence of any cutaneous manifestations of systemic sclerosis and a record of the morphology and distribution of the lesions were made.

The cutaneous features we looked for included -

Face;- radial furrows, beaked nose, inability to evert lower eyelid, smoothening of forehead expression, mouth opening, periorbital oedema and mask like facies

The cut off values for restricted mouth opening used in our study was 43mm in males and 37.6mm in females

Upper limbs;- digital ulcers, digital scars, pitting edema of fingers, sclerodactyly, gangrene, round finger pad sign, flexion contracture and cobblestone appearance.

Round finger pad sign refers to replacement of finger tip contour from peaked to hemisphere like tips.

Nails;- dystrophic nails, ragged cuticles, resorption of phalanges, pterygium inversum unguis

Lower limb;- leg ulcers, atrophie blanche and livedo reticularis

Other features looked for includes;-calcinosis, telangiectasias, pigmentary disturbances and presence of neck sign. Neck sign refers to the prominence of platysma on hyperextension of neck.

The extent and site of involvement of cutaneous sclerosis was noted in all patients. Modified Rodnan skin score(Annexure - III) was calculated to assess severity of disease for each patient at the time of first contact of the patient with the primary investigator.

Dermoscopy of the nail fold capillaries was performed using a Heine delta 20 dermoscope by examining all the finger nail folds after immersion with ultrasound gel. The most common nail fold capillary finding found among all digits was taken for analysis. The combination of abnormal findings seen in nail fold were also noted The abnormal capillary findings looked for included dilated capillaries, drop out, avascular pattern , giant capillaries and capillary haemorrhages. Capillary dilation

refers to enlargement of capillary lumen. Capillary drop out refers to focal areas of capillary loss and avascular areas to refers to multifocal or diffuse loss of capillaries.(89)Capillary haemorrhages refers to dotted or lined microhaemorrhage was located at periphery of capillaries. The capillary findings were classified on the basis of the classification devised by Cutolo et al. and Maricq et al. into normal pattern, scleroderma pattern and non specific type. (3) (87) (95)

(a) Normal pattern - homogenous capillary distribution without capillary loss in the nail plexus

(b) Scleroderma pattern - divided into 3 types based on classification by Maricq et al and Bergman et al.(96) (97) It is scleroderma pattern if it has two or more abnormalities.

i) early pattern – The early pattern has relatively preserved capillary architecture with no obvious capillary loss. There are few enlarged or giant capillaries with few capillary hemorrhages.

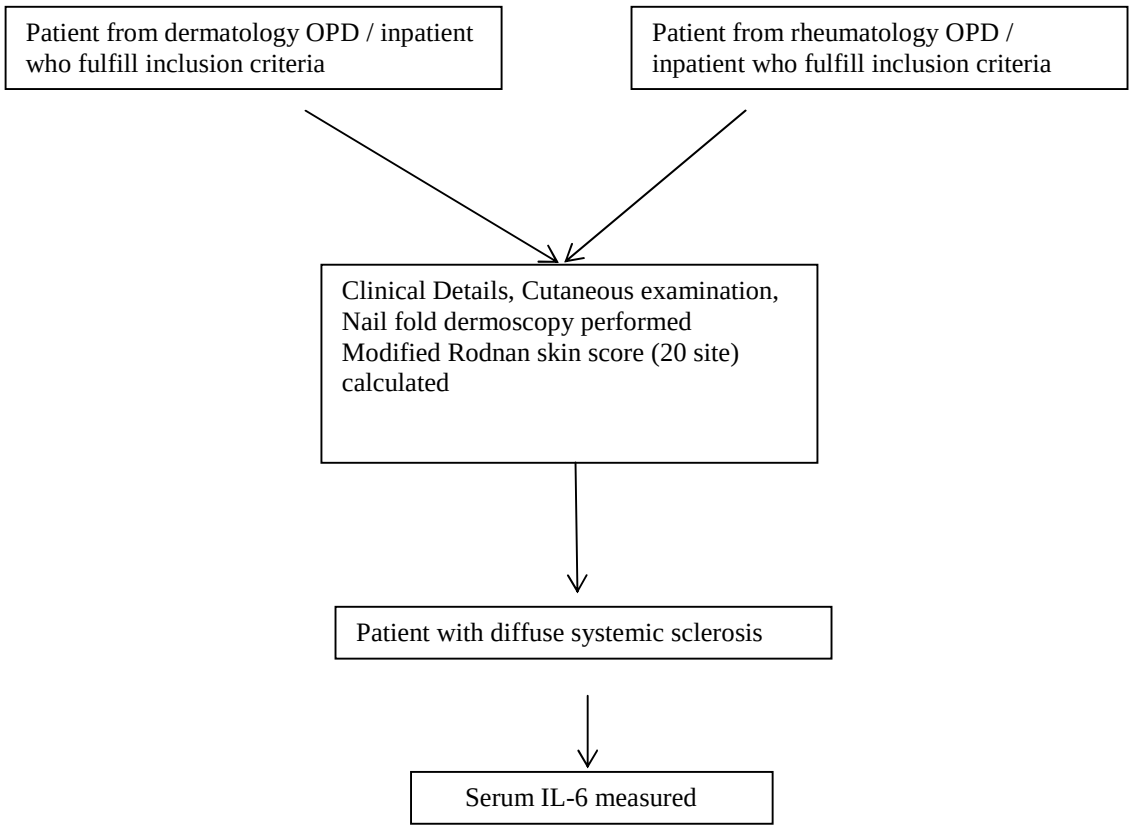
ii) Active pattern – There is moderate capillary loss with frequent giant capillaries and capillary hemorrhages.

iii) Late pattern – There is severe capillary disorganisation with severe loss of capillaries with large avascular areas. There are frequent ramified or bushy capillaries.

(c)Non specific type - The capillary changes don’t have the complete scleroderma pattern

Clinical photographs were taken using Sony Cybershot DSC-H55 camera. The diagrammatic algorithm of the study is shown in figure -4.

FIGURE 4 – DIAGRAMMATIC ALGORITHM OF THE STUDY



Investigations

1. *Serology* - ANA, anti topoisomerase and anti centromere antibodies were recorded

2. *HRCT chest and abdomen*

3. *Interleukin -6* - A blood sample was collected for measurement of serum interleukin 6 levels in a subset of patients with diffuse systemic sclerosis who were SCl-70 positive. Interleukin 6 levels were quantitated in the serum by the commercial available ELISA kit following manufacturer's protocol. ELISA was performed in duplicates i.e each samples was run in two wells and average was taken. Results were expressed as pg/ml and were treated as continuous variable.

   The other investigations like ECHO and barium swallow were done when indicated.

Sample Size

The sample size was calculated based on the study by Dogan et al.

The sample size was calculated presuming the frequency of nail fold dermoscopy finding as 50% and the sample size was calculated using the formula

$$N = \frac{4pq}{d^2}$$

p - 50 q - 50 d -10

$$N = \frac{4 \times 50 \times 50}{10 \times 10} = 100$$

Statistical Methods

The prevalence was expressed in terms of percentages along with 95% confidence intervals. The prevalence of the various cutaneous lesions in scleroderma was expressed as numbers and percentages. The association of dermoscopic capillary pattern and rodnan skin score with various clinical manifestations was evaluated using χ^2 tests. Epiinfo (version 7), a data management software was used for the data entry. SPSSPC version 21 was used for analysis.

Study Approval

This study was approved by the Institution Review Board (IRB No - 8594[observe]) (Annexure - 7)

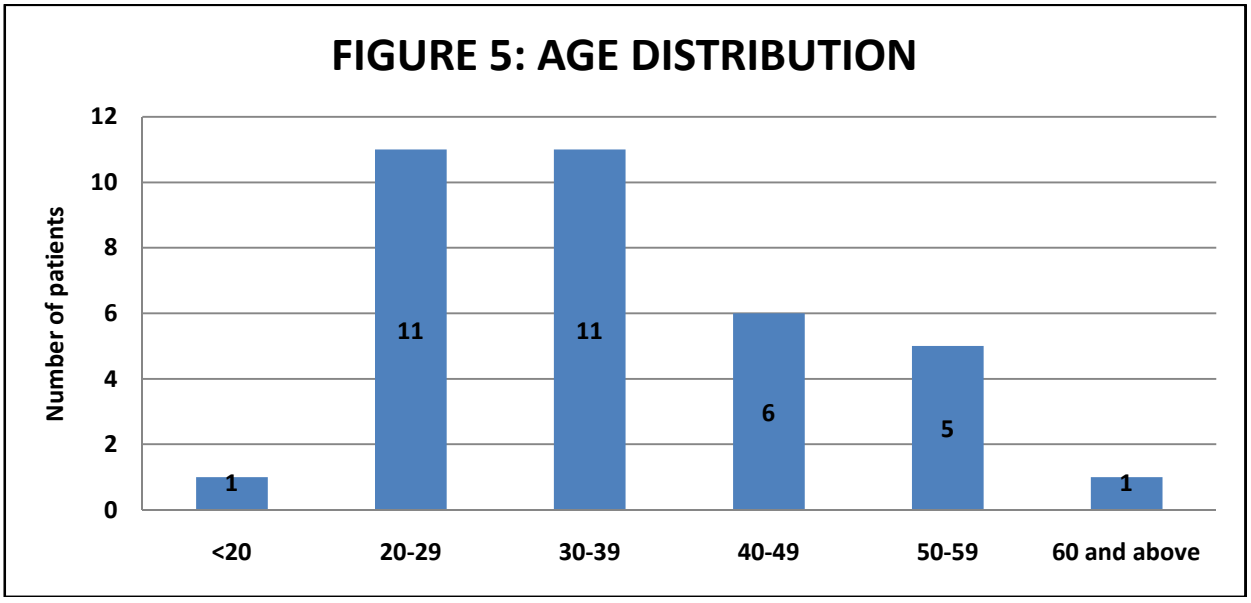
RESULTS

DEMOGRAPHIC PROFILE

Thirty five patients with the diagnosis of scleroderma were included in the study between February 2014 and September 2015. The characteristics of the study population have been described below.

AGE DISTRIBUTION

Age of the patients included in the study ranged from 17 and 62 years. The mean age was 36.29± 12 years and the median age 36 years. In the study population 63% were between 20 and 39 years of age. The age distribution of the patients is shown in figure -5.



SEX DISTRIBUTION

Out of the 35 patients included in the study, there was a female predominance with 30 (86%) females and 5 (14%) males in the study as shown in figure 6. The male to female ratio was 1:6.

FIGURE 6: SEX DISTRIBUTION

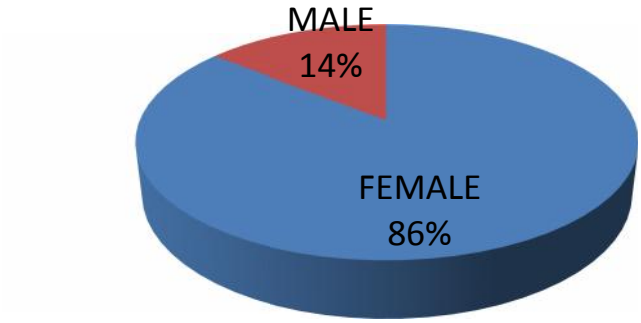
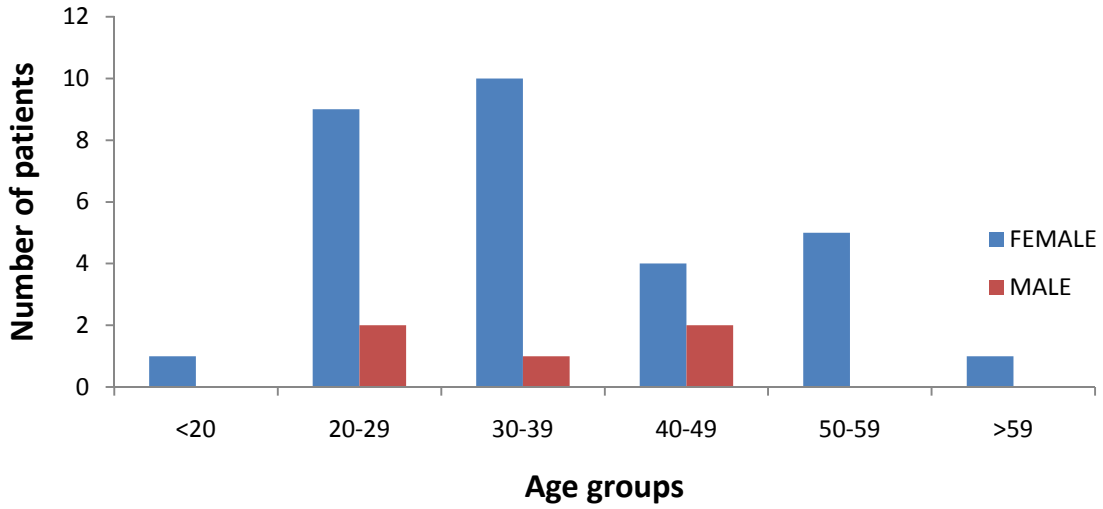


Figure 7 shows the age and sex distribution of the study population. Females outnumbered males in all the age groups. The majority of the females were present in the 30-39 age group (33.3%) followed by 20 – 29 (30%) age group. Of the 5 males in the study, 2 each (40%) were in the 20 -29 and 40-49 age group and one male was in the 30 to 39 years age group. There were no males below the age of 20 and above the age of 50 years.

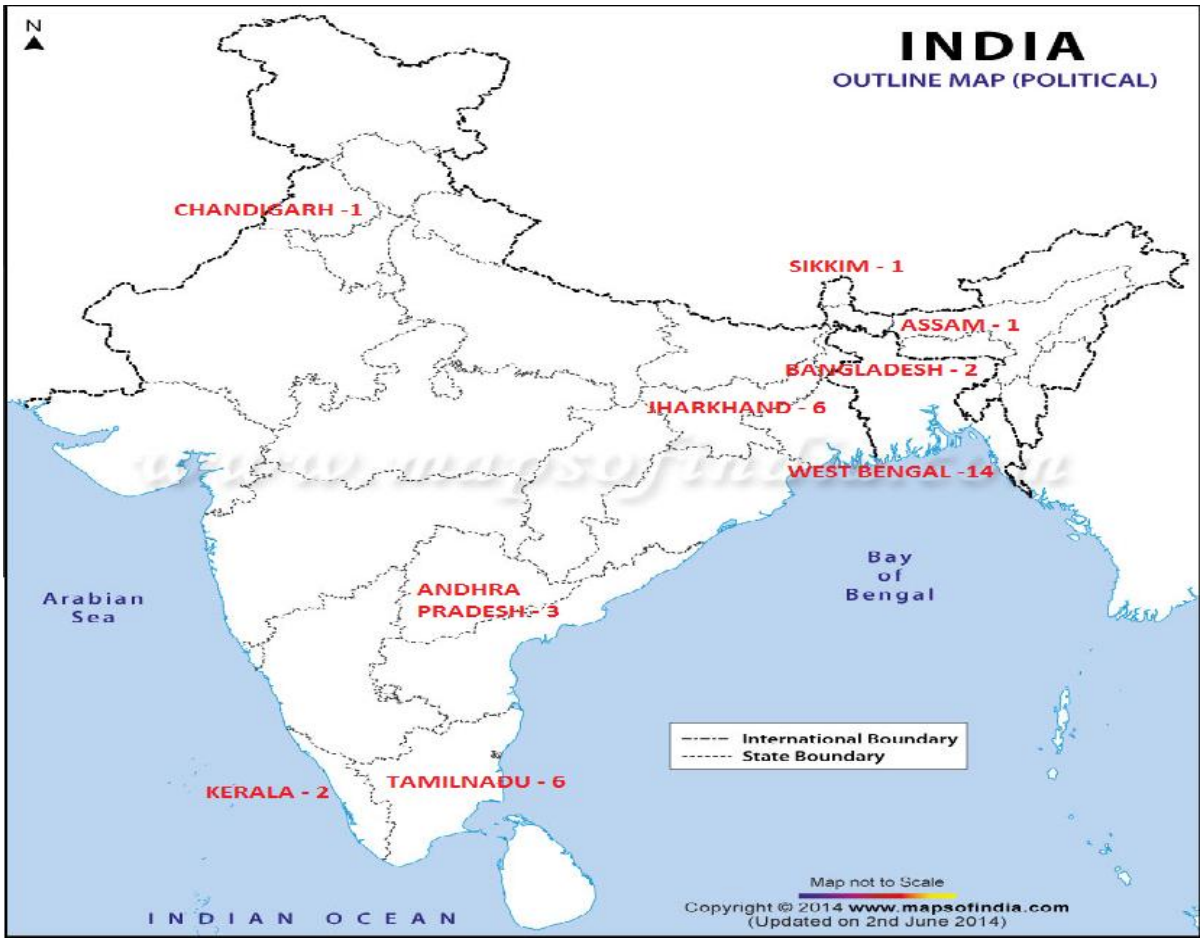
FIGURE 7 – AGE SEX DISTRIBUTION



GEOGRAPHICAL DISTRIBUTION

West Bengal accounted for 40% of the patients in the study followed by 6(17.1%) from Tamil Nadu and 5(14.3%) from Jharkhand. There were 2 patients from Bangladesh. Most of the cases were from the Eastern region of India contributing 68% of the study population as shown in figure 8.

FIGURE 8 – GEOGRAPHICAL DISTRIBUTION

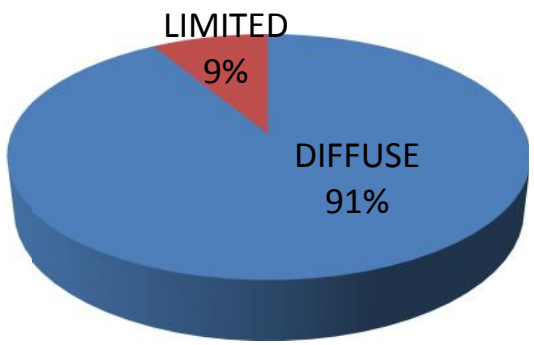


DISEASE CHARACTERISTICS

TYPE OF DISEASE

Scleroderma patients were classified into diffuse and limited based on the clinical and immunological characteristics. Majority (91%, n=32) of the patients had diffuse type of disease and only 9 %(n=3) had limited disease as shown in figure 9.

FIGURE 9 - EXTENT OF DISEASE



DURATION OF DISEASE

The mean duration of disease in the study population was 43.31± 31.8 months and the median was 36 months. The duration of the illness ranged from 4 to 120 months. There was a high proportion of patients with disease duration more than 5 years at the time of presentation (37.1%) as shown in table 4. This can be explained as most patients had initially presented in other settings prior to coming to our centre.

TABLE 4 : DURATION OF DISEASE

Duration of illness (months)	Frequency	percentage
< 12	4	11.4
12-23	6	17.1
24-35	7	20
36-47	3	8.6
48-59	2	5.7
>= 60	13	37.1

PRIOR TREATMENT RECEIVED

Duration of treatment among our study population is depicted in table 5.Among the 35 patients studied, 11 patients were treatment naïve. Among the 24 patients who had received prior treatment, the mean duration of treatment was 16.33± 15.1 months with the median duration being 9 months. The duration ranged from 1 to 48 months.

TABLE 5 - DURATION OF TREATMENT

Duration of treatment(months)	Frequency	Percentage
< 12	13	54.2%
12-23	3	12.5%
24-35	2	8.3
36-47	4	16.7%
48 and above	2	8.3%

The majority of patients were treated with systemic steroids either as prednisolone or deflazacort tablets or dexamethasone cyclophosphamide pulse therapy. Other immunosupressants that were commonly used were methotrexate and azathioprine Other drugs used included hydroxychloroquine and oral PUVAsol.

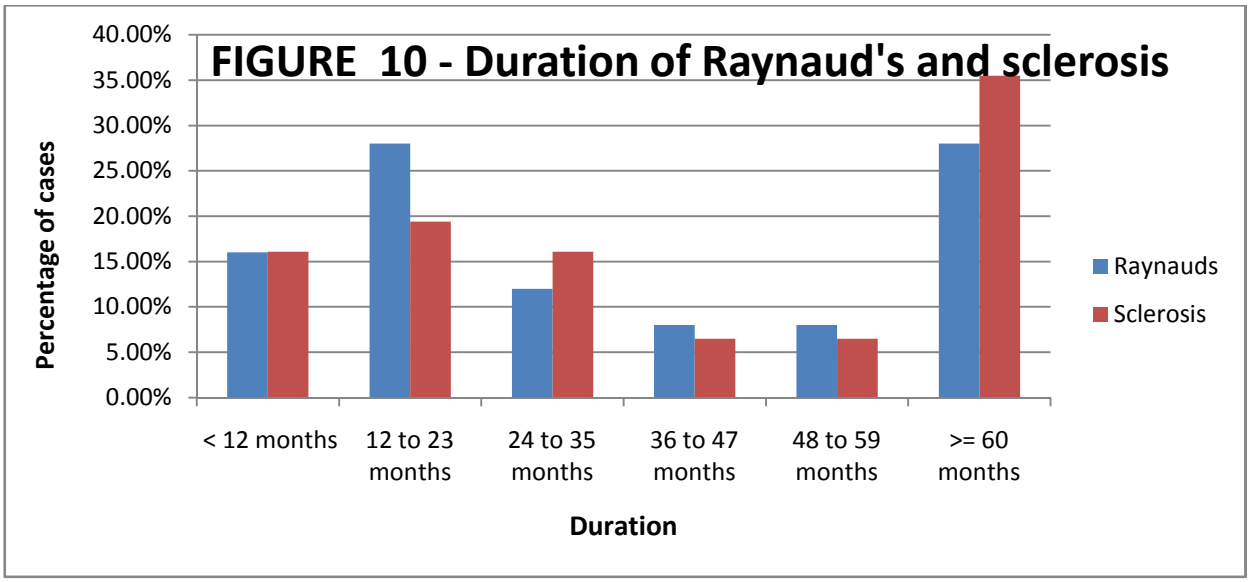
RAYNAUD'S PHENOMENON AND SKIN SCLEROSIS

The mean duration of Raynaud's phenomenon and skin sclerosis is shown in table 6 and figure 10 . The mean duration of Raynaud's phenomenon was 33.6±23.4 months and the median duration was 24 months. The duration ranged from 3 to 72 months. Four patients had onset of Raynaud's within one year of onset of disease. Of the 10

patients who did not present with Raynaud's phenomenon, 8 had diffuse systemic sclerosis and 2 had limited disease. The mean duration of skin sclerosis was 42.19± 34.03 months and the median was 29 months with duration ranging from 3 to 120 months. The duration of skin sclerosis was unknown in 4 patients. In our study population nine patients presented simultaneously with Raynaud's phenomenon and skin sclerosis.

TABLE 6 - DURATION OF RAYNAUD'S PHENOMENON AND SKIN SCLEROSIS

Duration in months	Raynaud's phenomenon		Sclerosis	
	Frequency	%	Frequency	%
< 12	4	16	5	14.2
12-23	7	28	6	17.1
24-35	3	12	5	14.2
36-47	2	8	2	5.7
48-59	2	8	2	5.7
>= 60	7	28	11	31.4
Unknown duration			4	11.4
Total	25		35	



CUTANEOUS MANIFESTATIONS

All the patients had cutaneous manifestations. Among the 35 patients, 30 had upper limb involvement and 3 had lower limb involvement. Facial involvement was present in 27 patients.

Table 7 depicts the cutaneous manifestations on the face. The commonest facial involvement was beaked nose which was present in 27 patients (77%) followed by radial furrows(71.4%). An inability to evert lower eyelid was present in 25 patients (71%). Mask like facies was present in 40% of our patients and only one patient presented with periorbital oedema. Mat like telangiectasia was present in 10 patients, most common site being the cheeks. All the patients with mat like telangiectasias had diffuse systemic sclerosis.

TABLE 7 –CUTANEOUS MANIFESTATIONS - FACE

Clinical features	**Frequency**	**Percentage**
Beaked nose	27	77.1
Radial furrow	25	71.4
Inability to evert lower eyelid	25	71.4
Smoothening of forehead expression	18	51.4
Mask like facies	14	40
Peri- orbital edema	1	2.9

The mouth opening measurement in our study population is depicted in table- 8. The mean mouth opening which was measured as inter incisor distance was 43.97 mm and the median 42 mm. The minimum was 20 mm and the maximum 64 mm. Reduced mouth opening was present in 54.3% (n=19) of our study population. The normal mouth opening in an Indian population was 51.3±8.3mm in males and 44.3±6.7 in females. The cut off values used in our study was 43mm in males and 37.6mm in females. (98)

TABLE 8 - MOUTH OPENING

MOUTH OPENING (mm)	Number	Percentage
< 30	8	22.9
30-39	9	25.7
40-49	7	20
50-59	2	5.7
>= 60	9	25.7

The cutaneous manifestations in the upper and lower limbs are shown in table 9. The commonest cutaneous manifestation in the fingers were sclerodactyly (85.7%) followed by digital pitted scars (51.4%). Digital ulcers and gangrene of the fingers were seen only in one patient each. In the study population, 7 patients had flexion contractures with fingers being involved in 3 patients and the elbows and hands being involved in 2 patients each. Round finger pad sign was seen in 9 patients. The commonest site of round finger pad sign was ring finger (55.6%) followed by the index and middle finger. The commonest manifestation in the nail was ragged cuticles (65.7%) followed by pterygium inversum unguis (17.1%). Apart from skin sclerosis, the lower limbs were involved in 4 cases with either leg ulcers or atrophie blanche.

Table 9–SKIN LESIONS OF UPPER LIMB AND LOWER LIMBs

Clinical Features	**Frequency**	**Percentage**
Digital ulcer	1	2.9
Digital scar	18	51.4
Pitting edema fingers	2	5.7
Round finger pad sign	9	25.7
Ring finger	*5*	
Middle finger	*2*	
Index finger	*2*	
Flexion contractures	7	20
Fingers	*3*	
Elbow	*2*	
Hand	*2*	
Sclerodactyly	30	85.7
Gangrene	1	2.9
Cobblestone appearance	1	2.9
Nails		
Dystrophic nails	4	11.4
Ragged cuticles	23	65.7
Resorption of phalanges	5	14.3
Pterygium inversum unguis	6	17.1
Lower limb		
Leg ulcer	3	8.6
Atrophie blanche	1	2.9

PIGMENTARY DISTURBANCES

Pigmentary disturbances were noted in 33 subjects (94.3%). Hyperpigmentation was seen in 27 subjects, salt and pepper pigmentation in 23 and depigmentation in 17. There were 17 subjects with only one pigmentary disturbance, 9 subjects with 2 pigmentary abnormalities and 7 subjects with all three abnormalities. Table -10 shows the frequency of the various pigmentary disturbances.

TABLE 10 –TYPE OF PIGMENTARY DISTURBANCE

Pigmentation	Frequency	Percentage
Salt and Pepper pigmentation	23	65.7
Depigmentation	17	48.6
Hyperpigmentation	16	45.7

Table-11 shows the distribution of the pigmentary disturbances. Hyperpigmentation was commonest in the upper limb (37%) followed by the face (22.2%). Generalised hyperpigmentation was present in 3 patients. Salt and pepper pigmentation was most commonly present in the trunk (16.98%) and back (16.98%). Three patients had salt and pepper pigmentation in the retro-auricular region. The face (27.6%) was the commonest site of involvement for depigmentation.

TABLE 11 – SITE OF PIGMENTARY DISTURBANCES

Site	Depigmentation(no.)	%	Hyperpigmentation (no.)	%	Salt and pepper pigmentation	%
Generalized	-		3	11.1	-	
Neck	4	13.8	2	7.4	6	11.3
Upper limb	5	17.2	10	37	10	18.87
Face	8	27.6	6	22	6	11.3
Back	2	6.9	-	9	9	16.98
Ear	3	10.3	-		1	1.89
Lower limb	3	10.3	3	11.1	1	1.89
Trunk	4	13.8	3	11.1	9	16.98
retroauricular	-		-		3	5.66
Scalp	-		-		8	15.1

SKIN SCLEROSIS

Site of skin sclerosis and modified Rodnan skin scores are shown in table 12 and 13. Cutaneous sclerosis was present in 97.1% of the patients. The commonest site of cutaneous sclerosis was the upper limb (n=34) followed by lower limb (n=19) and face (n=18).

Table 12 - SITE OF SCLEROSIS

Site	Frequency	Percentage
Face	18	52.9
Upper limb	3	100
Chest	10	29.4
Abdomen	4	11.8
Lower limb	19	55.9

MODIFIED RODNAN SKIN SCORE

Skin sclerosis was assessed using the modified Rodnan skin score. The modified Rodnan skin score ranged from 0 to 48. The mean score was 16.66± 10.9 and the median was 15.

TABLE 13 – MODIFIED RODNAN SKIN SCORE

RODNAN SKIN SCORE	Frequency	Percentage
< 10	14	40
10-19	9	25.7
>=20	12	34.3

Calcinosis was present in only 3 patients with diffuse disease. Neck sign was present in 20 patients (57.1%). Cobblestone appearance over the neck was present in one patient(2.9%). Other cutaneous manifestations were seen in 3 patients. These included melanonychia, melasma and scarring alopecia with depigmentation over the scalp in one patient each.

COMPARISONS BETWEEN LIMITED AND DIFFUSE SYSTEMIC SCLEROSIS

The clinical manifestations in diffuse and limited systemic sclerosis are compared in table 14. In diffuse systemic sclerosis beaked nose, radial furrows and inability to evert eyelid were the commonest cutaneous manifestations. In the limited type of disease facial involvement was present in only one patient who had beaked nose, radial furrows and inability to evert eyelid. The only upper limb manifestation in limited disease is sclerodactyly which was present in all the patients. The nail involvement of limited disease was ragged cuticles seen in one patient. Lower limb involvement, neck signs, calcinosis and telangiectasia were absent in the limited sclerosis group.

TABLE 14 – CUTANEOUS MANIFESTATIONS – DIFFUSE AND LIMITED

Features	Diffuse (n=32)		Limited (n=3)	
	Number	percentage	Number	Percentage
Face				
Radial Furrows	24	75	1	33.3
Beaked nose	26	81.3	1	33.3
Inability to evert eyelid	25	78.1	1	33.3
Smoothening of forehead expression	18	56.3	0	
Mask like facies	14	43.8	0	
Peri-orbital edema	1	3.1	0	
Extremities				
Digital ulcer	1	3.1	0	
Digital pitted scars	18	56.3	0	
Pitting edema of fingers	2	6.3	0	
Round finger pad sign	9	28.1	0	
Flexion contractures	7	21.9	0	
Sclerodactyly	27	84.4	3	100
Gangrene	1	3.1	0	
Nails				
Dystrophic nails	4	12.5	0	
Ragged cuticles	22	68.8	1	33.3
Resorption of phalanges	5	15.6	0	
Pterygiuminversum unguis	6	18.8	0	
Cobblestone appearance	1	3.1	0	

SYSTEMIC MANIFESTATIONS

The systemic manifestation in systemic sclerosis in our study population is depicted in table 15. The commonest affected internal organ was lung which presented with interstitial lung disease in 78.1% of the patients. The second commonest involved system was the gastrointestinal system which presented as oesophageal reflux in 46.9% followed by oesophageal dysmotility in 28.1%. The cardiac involvement included ventricular premature complexes, mitral and tricuspid regurgitation and anterior wall myocardial infarction. One patient presented with proteinuria. Myositis was present in 4 patients .None of the patients with limited scleroderma had systemic manifestations. Other systemic manifestations include hypothyroidism in 2 patients and osteoporosis in 2 patients.

TABLE 15 – SYSTEMIC MANIFESTATIONS

Features	Diffuse (n=32)	
	Frequency	%
Oesophageal dysmotility	9	28.1
Oesophageal reflux	15	46.9
Interstitial lung disease	25	78.1
Pulmonary artery hypertension	1	3.1
Cardiac	5	15.6
Renal	1	3.1
Muscle	4	12.5

ASSOCIATION OF MODIFIED RODNAN SKIN SCORE WITH SYSTEMIC MANIFESTATIONS

The systemic involvement in our patients with various ranges of Rodnan skin score is shown in table 16. A significant association (p=0.026) was noticed between the Rodnan skin score and interstitial lung disease. There was no association noticed between the Rodnan skin score and oesophageal dysmotility or with oesophageal reflux.

TABLE 16 -ASSOCIATION OF RODNAN SKIN SCORE WITH SYSTEMIC MANIFESTATIONS

RODNAN SKIN SCORE	INTERSTITIAL LUNG DISEASE No (%)	OESOPHAGEAL DYSMOTILITY No (%)	OESOPHAGEAL REFLUX No (%)
<10	8(57.1)	3(21.4)	5 (35.7)
10-19	5(55.6)	4(44.4)	5(55.6)
>19	12(100)	2(16.7)	5(41.7)
TOTAL	25	9	9
P value	0.026	0.316	0.640

Table 17 shows association of modified Rodnan skin score with type of the systemic sclerosis. There was an increasing trend between the Rodnan's skin score and extent of disease (χ^2 =4.922 df =2 p = 0.086). This however was not statistically significant.

TABLE 17 -ASSOCIATION OF RODNAN'S SKIN SCORE WITH TYPE OF DISEASE

RODNAN SKIN SCORE	TYPE OF DISEASE		TOTAL
	DIFFUSE No.(%)	LIMITED No.(%)	
<10	11(78.6)	3(21.4)	14
10-19	9(100%)	0	9
>19	12(100%)	0	12
TOTAL	9	26	35

DERMOSCOPY

The various nail fold dermoscopic findings in our study population were noted in table 18. The commonest dermoscopic feature was dilated capillaries (91.4%) followed by dropouts (62.9%).

TABLE 18 – DERMOSCOPY FEATURES

Feature	Frequency (%)	Percentage
Dilated Capillaries	32	91.4
Giant Capillaries	15	42.9
Avascular Areas	11	31.4
Capillary haemmorhages	16	45.7
Dropouts	22	62.9

The nail fold dermoscopic features present in diffuse and limited systemic sclerosis are depicted in table 19. In the limited disease the commonest dermoscopic feature was dilated capillaries with preserved capillary configuration.

TABLE 19 – DERMOSCOPY FEATURES - DIFFUSE VS LIMITED

Feature	Diffuse		Limited	
	Frequency	Percentage	Frequency	Percentage
Dilated Capillaries	29	90.6	3	100
Giant Capillaries	14	43.8	1	33.3
Avascular Areas	11	34.4	0	
Capillary hemorrhages	15	46.9	1	33.3
Dropouts	22	68.8	0	

Table 20 shows the distribution of abnormal capillary patterns. In our study we noticed single abnormal finding in 7 patients with commonest pattern being dilated

capillaries, two abnormal findings in 11 patients with commonest pattern being capillary dilatation with drop outs, three abnormal findings in 10 patients commonest being capillary dilatation and drops outs with capillary haemorrhage or giant capillaries and four abnormal findings in 5 patients and all five abnormal findings in 2 patients.

TABLE 20 – DISTRIBUTION OF ABNORMAL DERMOSCOPY PATTERN

ABNORMAL DERMOSCOPY PATTERNS	number	Percentage
Single finding (n=7)		
Dilated capillaries	4	11.4
Drop out	2	5.7
Avascular	1	2.9
Two findings(n=11)		
Dilated capillaries and giant capillaries	2	5.7
Dilated capillaries and capillary hemorrhage	1	2.9
Dilated capillaries and dropout	8	22.9
Three findings(n = 10)		
Dilated capillaries, giant capillaries and capillary hemorrhage	2	5.7
Dilated capillaries, giant capillaries and avascular areas	1	2.9
Dilated capillaries, capillary hemorrhage and dropout	3	8.6
Dilated capillaries giant capillaries and dropouts	3	8.6
Avascular, dilated capillaries and capillary hemorrhage	1	2.9
Four findings (n= 5)		
Dilated capillaries, giant capillaries, avascular areas, capillary hemorrhage	2	5.7
Dilated capillaries, avascular, capillary hemorrhage and dropout	3	8.6
All findings(n=2)		
Dilated capillaries, giant capillaries,avascular, capillary haemmorhage, dropout	2	5.7

Nail fold capillary pattern

The nail fold pattern was classified into early, active, late scleroderma pattern and non specific pattern by Cutolo et al. The nail fold capillary patterns which were seen in our study population are seen in table 21. Scleroderma pattern was present in 77.1% of the study population and non specific pattern was present in 22.9%. Among the patients with scleroderma pattern 5 had early pattern, 15 had active pattern and 7 had late pattern.

TABLE 21 –NAILFOLD CAPILLARY PATTERN

Capillary Pattern	Frequency
Early	5
Active	15
Late	7
Non specific	8
Total	35

ASSOCIATION OF MEAN DURATION OF DISEASE WITH TYPE OF CAPILLARY PATTERN

Table 22 depicts the mean duration of disease with type of capillary pattern. It shows the mean duration of illness is less in patient with early scleroderma as compared to patients with active and late pattern.

TABLE 22– DERMOSCOPY PATTERN AND MEAN DURATION OF DISEASE

DERMOSCOPY PATTERN	MEAN DURATION(MONTHS)
Early	32.4±23.8
Active	44.80±30.4
Late	46.29±29.2
Non specific	44.75±43.5

ASSOCIATION OF TYPE OF DERMOSCOPY CAPILLARY PATTERN WITH SYSTEMIC MANIFESTATIONS

The association of type of dermoscopic pattern with systemic manifestation are shown in Table 23. In patients with interstitial lung disease the commonest dermoscopy feature was active pattern followed by late pattern. Even though larger proportion of patients with interstitial lung disease had scleroderma pattern, the association was not statistically significant. This could possibly be due to smaller sample size**.** In patient with oesophageal dysmotility the commonest observed pattern was active with no statistically significant association. In oesophageal reflux, the commonest observed pattern was active pattern followed by non specific pattern. In patients with cardiac involvement active and late pattern were the commonest observed patterns. All patients with muscular system involvement had scleroderma pattern with commonest being the active type. As only one patient each had pulmonary artery hypertension and renal involvement, these were not correlated.

TABLE 23- ASSOCIATION OF TYPE OF DERMOSCOPY CAPILLARY PATTERN WITH SYSTEMIC MANIFESTATIONS

Type of scleroderma	Interstitial lung disease No(%)	Esophageal Dysmotility No(%)	Esophageal reflux No(%)	Cardiac No(%)
Active	13(86.7)	6(40)	7(46.7)	2(13.3)
Early	3(60)	1(20)	2(40)	1(20)
Late	5(71.4)	0	2(28.6)	2(28.6)
Non-specific	4(50)	2(25)	4(50)	0
Total	25	9	15	5
p value	0.281	0.249	0.836	0.45

Table -24 shows the association of type of dermoscopy capillary pattern with Raynaud's phenomenon. There was no association between type of capillary pattern and Raynaud's phenomenon

TABLE 24 - ASSOCIATION OF TYPE OF DERMOSCOPY CAPILLARY PATTERN WITH RAYNAUD'S PHENOMENON

Dermoscopy capillary pattern	Raynauds phenomenon Present No(%)	Raynauds phenomenon absent (No%)	Total
Active	11(73.3)	4(26.7)	15
Early	5(100)	0	5
Late	4(57.1)	3(42.9)	7
Non-specific	3(37.5)	5(62.5)	8
Total	25	10	35

χ^2= 3.039 df=3. P = 0.644

INVESTIGATIONS

ANTI NUCLEAR ANTIBODY PATTERNS

ANA was positive in 31 patients and not done in 4 patients. The commonest type was speckled (35.5%) followed by speckled and nucleolar (25.8%).

TABLE 25- ANA PATTERNS

Patterns of ANA	Frequency (%)
Nucleolar	4 (12.9)
Speckled	11(35.5)
Speckled and nucleolar	8(25.8)
Not specified	8(25.8)

Anti CENP was positive in all the patients with limited disease. Anti Scl -70 was positive in 19 (59.3%) of our study population.

COMPUTED TOMOGRAPHY - CHEST

Abnormal features in CT thorax were shown in table 26. The commonest feature was interstitial lung disease which manifested as ground glass opacities or NSIP pattern.

TABLE 26 – CT findings

CT findings	Frequency(n-13)
Normal	3(23.1)
Interstitial lung disease	8(61.5)
Dilated oesophagus	2(15.3)
Liver heterogeneity	1(7.7)

INTERLEUKIN -6 LEVELS

Interleukin -6 was performed in a subset of 7 patients with scl-70 positive diffuse systemic sclerosis. Of the 7 patients, 2 patients had elevated interleukin 6 levels.

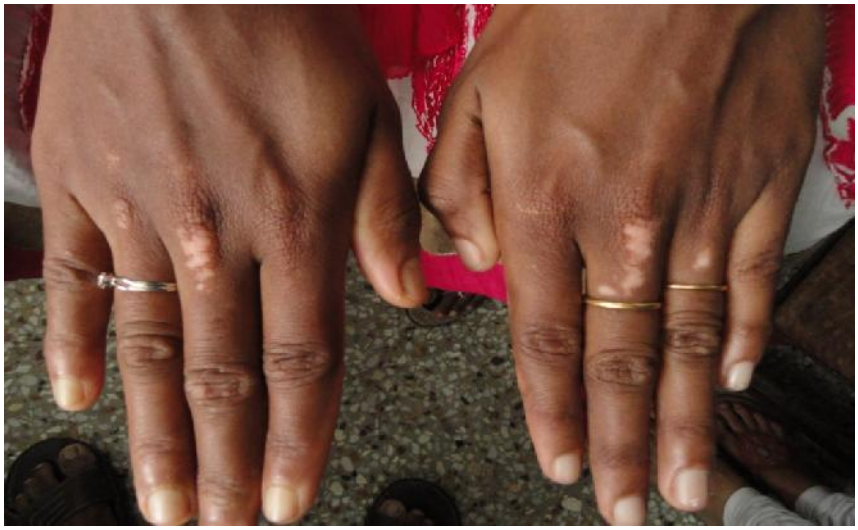


FIGURE 11- depigmented macules over the dorsa of hand

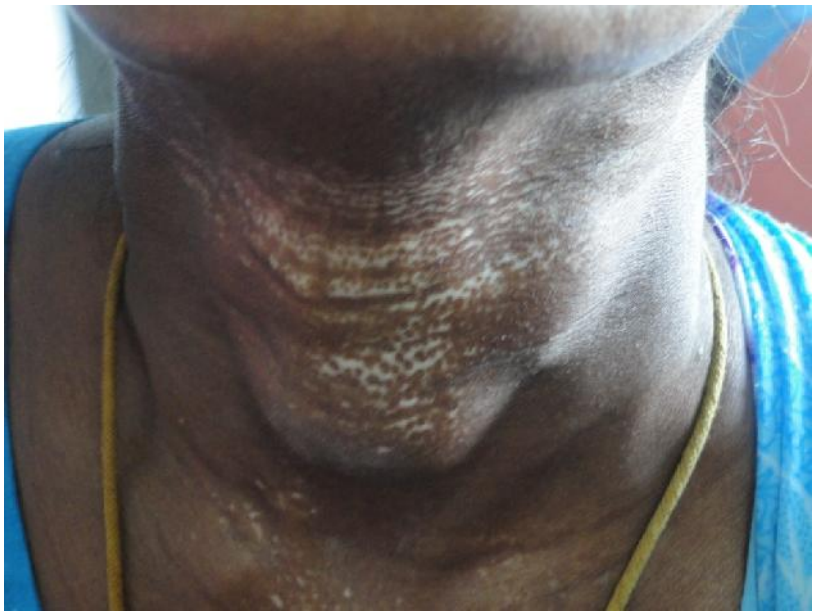


FIGURE 12 - salt and pepper pigmentation over the neck

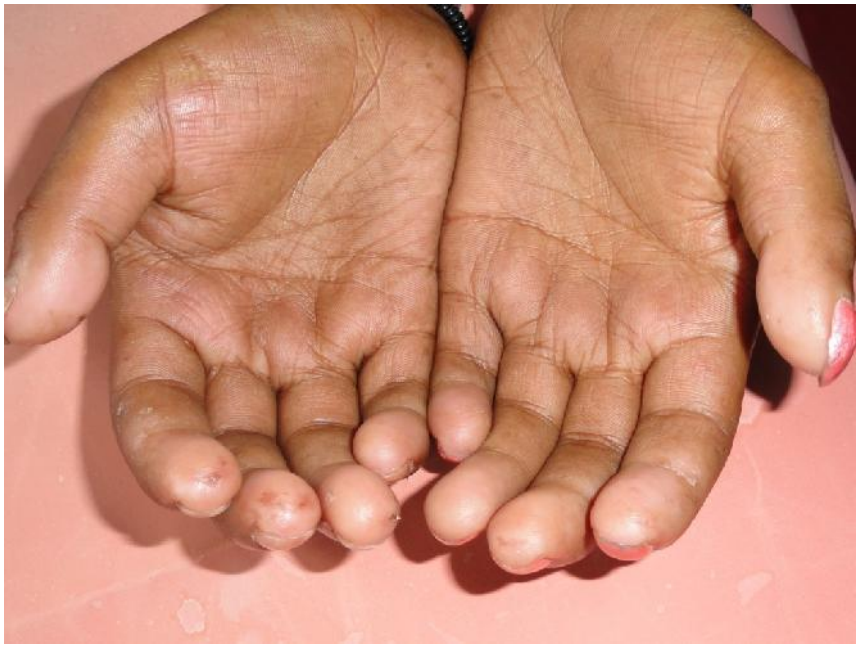


FIGURE 13 - digital scars over the finger tips

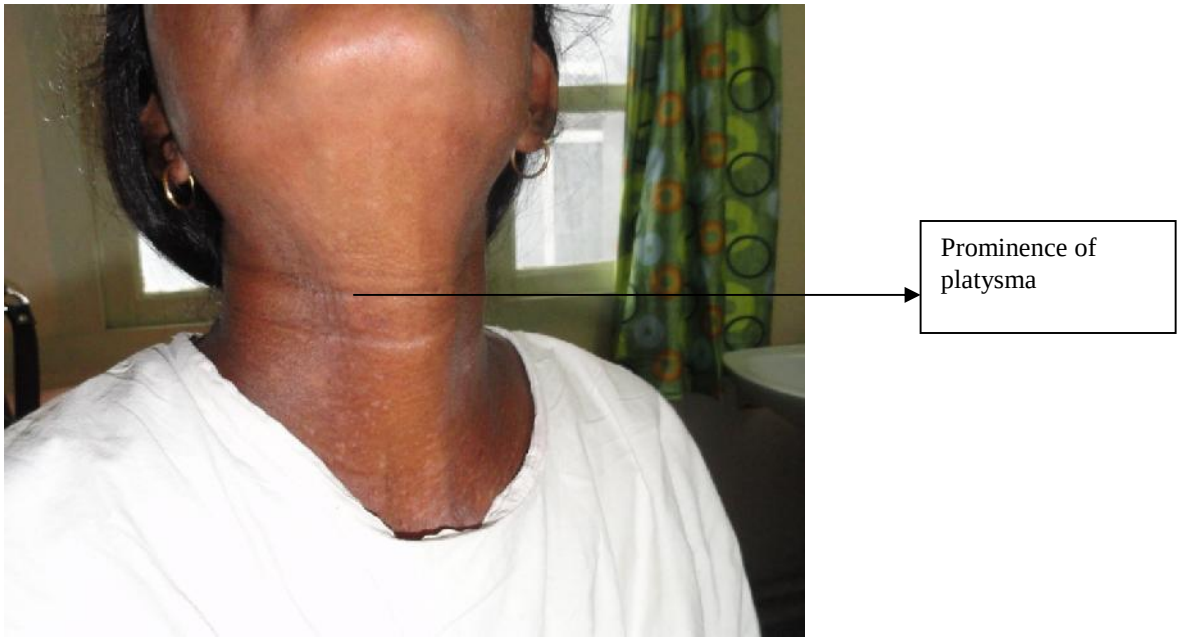


FIGURE 14 - neck sign

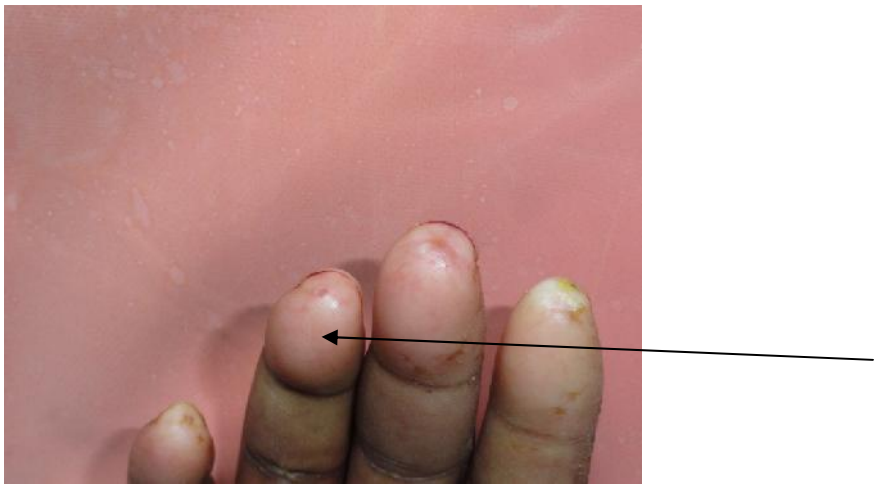


FIGURE 15- Round finger Pad sign

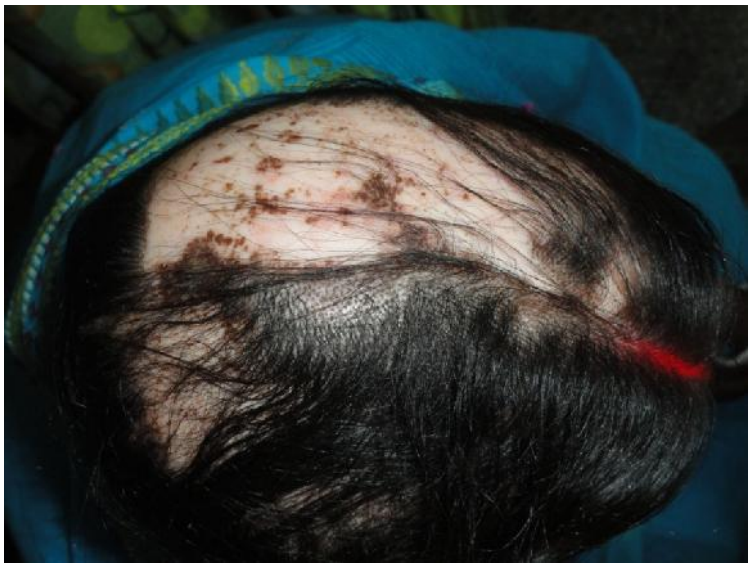


FIGURE 16- Scarring alopecia with depigmentation – scalp

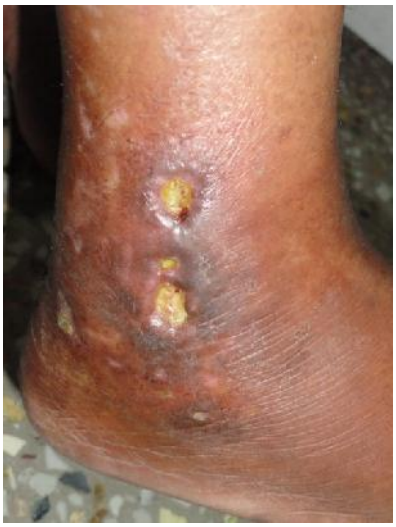


FIGURE 17 - ulcers over right ankle

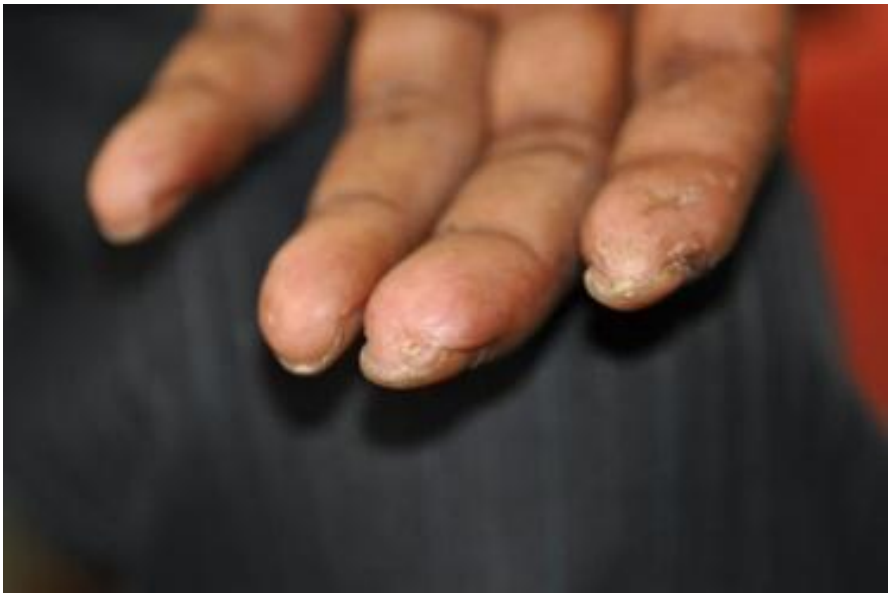


FIGURE 18 – pterygium inversum unguis

FIGURE 19 - Mask like facies

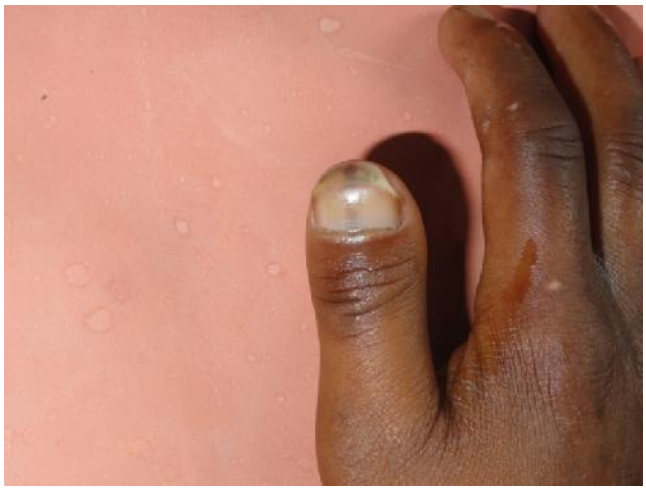


FIGURE 20 - melanonychia – right thumb nail

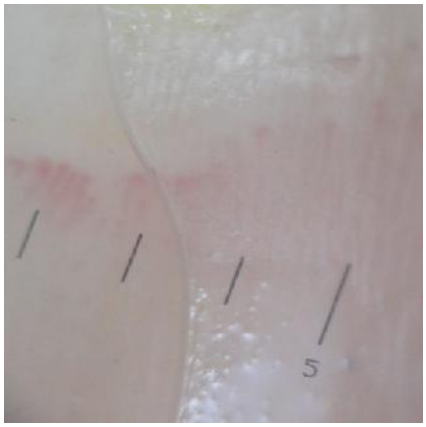


FIGURE 21 – Early scleroderma pattern :dilated capillaries with normal capillary configuration

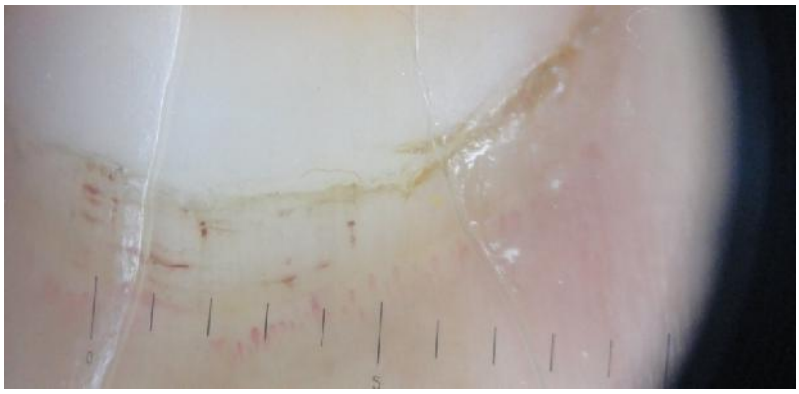


FIGURE 22 – Active scleroderma pattern: dilated capillaries, drop outs, haemorrhage

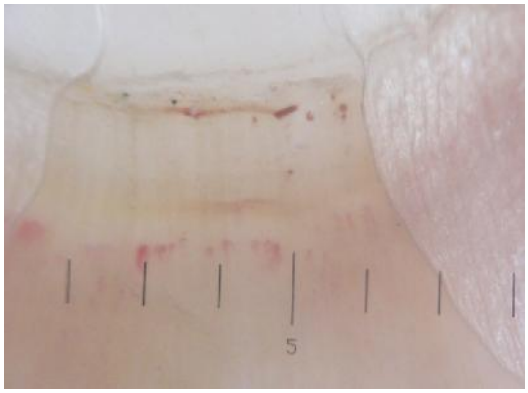


FIGURE 23 – Active scleroderma pattern: giant capillaries, dilated capillaries , dropout, capillary haemorrhage

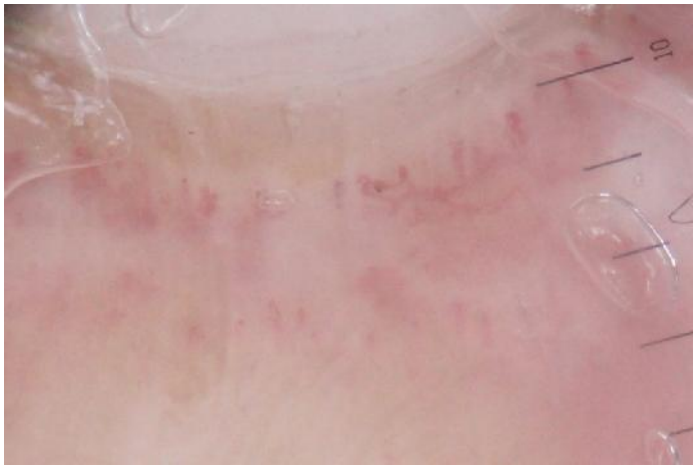


FIGURE 24 - Active scleroderma pattern : dilated capillaries, ramifications, drop out, giant capillaries

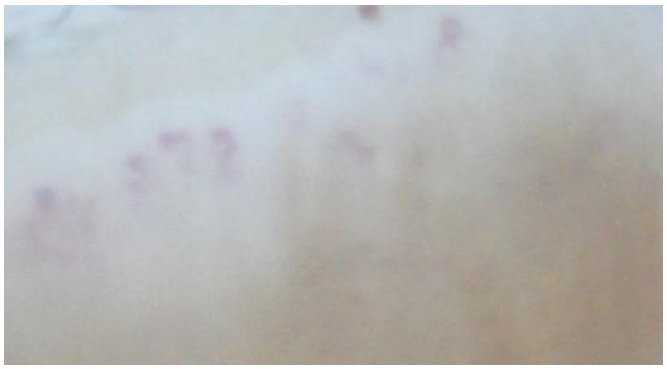


FIGURE 25 - Active scleroderma pattern: giant capillaries , drop out

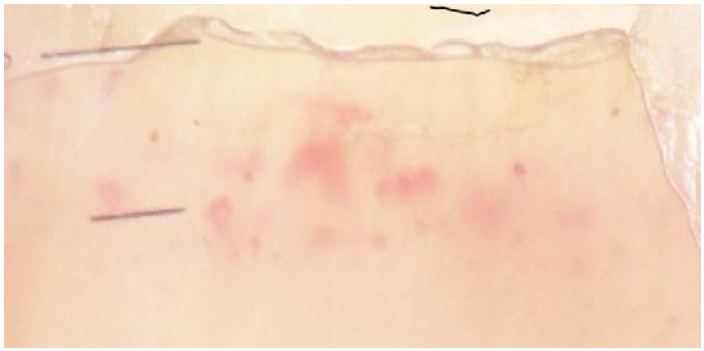


FIGURE 26 - Active scleroderma pattern: dilated capillaries, bushy capillaries haemorrhages, avascular areas

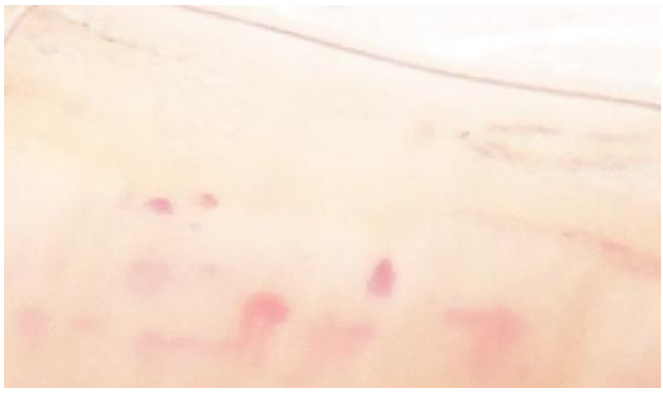


FIGURE 27 - Active scleroderma pattern: dilated capillaries, bushy capillaries haemorrhages, avascular area

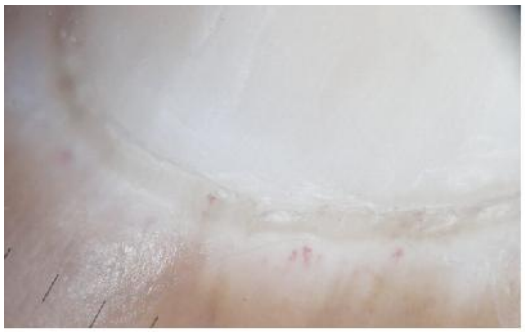


FIGURE 28 - late scleroderma pattern : avascular areas with dilated capillaries

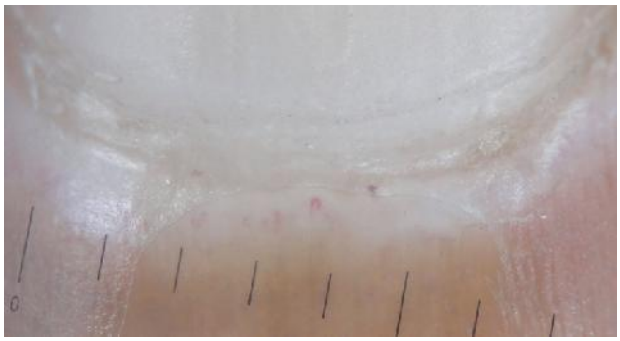


FIGURE 29 – late scleroderma pattern : Avascular areas with dilated capillaries

DISCUSSION

Scleroderma is an autoimmune condition of unknown aetiology. It is characterised by skin thickening and fibrosis of visceral organs including the lungs, gastrointestinal tract, and heart. Raynaud's phenomenon and immune system activation is manifested by presence of SSc-related antibodies, in particular anti-centromere antibodies and anti-topoisomerase I (also called Scl-70) antibodies. (2) In the latest ACR – EULAR classification nail fold dermoscopy is one of the criteria for the diagnosis of scleroderma. (48) There are no prior studies on dermoscopic patterns in our Indian setting. Hence we proposed to study the cutaneous profile and nail fold dermoscopy of all patients who presented with scleroderma in our setting.

Thirty five patients were recruited in the study from February 2014 to September 2015. All patients with diffuse disease fulfilled the ACR criteria and patients with limited disease had sclerodactyly with CENP antibody positivity.

Demographic profile

Male: female ratio

In our study there was a female preponderence with male to female ratio being 1:6. This was similar to the study in Britain by Silman et al.(1:6) and with an Indian study by Sharma et al. (1:5.2).(99)(8)However the female gender predisposition was higher than the study in United States by Mayes et al.(1:4) and the study in Australia by Robert Thomson et al. (1:4).(5)(10) It was lower than the study in Iceland by Geirsson et al. (1:8) and the study in Japan by Tamaki et al. (1:14).(9) (11)

Age

The mean age in our study was 36.29± 12 years which was almost similar to the study done by Sharma et al and Ruangjutipopan et al., but lower than the study by Reville et al.(78)(8)(5)

Duration of disease

The mean duration of our disease was 43.31± 31.8 months which was similar to the study done by Pradhan et al. but shorter than the study done by Sharma et al.(8)The duration of disease among the African American was 30±20 months and whites was 21± 18 months.(59)Our patients had a longer duration of disease compared to the studies.

Geographical distribution

In our study we observed that majority of the patients(68%) were from the eastern region followed by the southern states. The patients from the northern, western and central region were limited.

Type of disease

The prevalence of diffuse disease was higher in our study in comparison to the study by Pradhan et al and Reville et al. The prevalence of limited disease in our study was less(9%) as compared to the study by Pradhan et al which was 29.1%. (59)(12)

The clinical features of our study were compared with clinical features in other Indian studies in various geographical locations as depicted in table -27. There were

no prior studies done on cutaneous manifestations in the eastern region of India. Cutaneous sclerosis was present in 97.1% of individuals which was similar to the studies by Sharma et al. and Krishnamurthy et al. and higher than the study by Pradhan et al. Presence of Raynaud's phenomenon was similar to the study by Pradhan et al. The study by Sharma et al. had a higher prevalence(98.5%) and Krishnamurthy et al.(28.2%) had a lower prevalence of Raynaud's phenomenon. The lower prevalence in the study by Krishnamurthy et al. was attributed to the hot climate. The prevalence of Raynaud's phenomenon in our study was higher as ours being a tertiary centre caters to patients from all parts of India.

Pigmentary disturbances were higher in our study as compared to other studies. (8)(50) Salt and pepper pigmentation was the commonest type of pigmentation in our study as compared to hyperpigmentation in the study by Sharma et al. Digital ulcers, gangrene, resorption of digits and flexion contractures were less common in our study as compared to the other Indian studies. The commonest site of flexion contracture was the fingers which was similar to the study by Sharma et al. Telangiectasias were less common in our study as compared to the study by Sharma et al.(26.8% vs 36.8%). Mean mouth opening in our study was higher (43.97$\pm$13.66mm) as compared to the north Indian study in which mean mouth opening was 24.6±19.01 mm.. Reduced mouth opening was present in 54.3%. Mean value of modified Rodnan skin scores in our study was 16.66$\pm$ 10.9 which was lower than the study by Sharma et al. and similar to the west. The decrease in Rodnan score

in our study as compared to other Indian studies can be explained by the fact that most patients were on prior treatment before coming to our centre. In our study upper limb was the commonest site of cutaneous involvement and scelerodactyly was the commonest manifestation. Round finger pad sign was present in 7 of our study population with the commonest site being the ring finger. The commonest manifestations in the nails were ragged cuticles which were seen in 65.7% and pterygium inversum unguis which was seen in 17.1%. There were no studies from India looking at nail manifestations in systemic sclerosis.

Leg ulcers were seen in 3 patients and cobblestone appearance over neck was seen in one patient. Sclerodactyly was present in all patients with limited disease. Calcinosis and telangiectasis, which are commonly associated with limited type of disease was conspicuously absent in our subset of patients with limited disease. We had only 3 patients with limited disease and hence, a definite conclusion cannot be drawn. In the limited disease all the patients had sclerodactyly. Facial involvement was present in one patient who had beaked nose, radial furrows and inability to evert lower eyelid. A significant association (p=0.026) was found between Rodnan skin score and interstitial lung disease. This was in keeping with other studies which proved a positive association between type and extent of disease and interstitial lung disease. (12)(8)(50)

TABLE 27 - CLINICAL FEATURES IN VARIOUS INDIAN STUDIES

Feature	Our study	Sharma et al. (8)	Krishnamurthy et al. (50)	Pradhan et al. (12)
No. of patients	35	100	78	110
Skin sclerosis	97.1	98.5	100	74.1
Raynaud's Phenomenon	71.4	98.5	28.2	76.5
Telangiectasia	28.6	36.8	-	-
Pigmentary disturbance	94.3	91	73.1	-
Hyperpigmentation	45.7	88.1	-	-
Salt and pepper pigmentation	65.7	55.3	-	-
Depigmentation	48.6	31.3	-	-
Gangrene	2.9	6.7	-	-
Flexion contracture	20	64.6		-
Digital ulcer	2.9	58.6	47.4	23.5
Resorption of digits	14.3	46.6	7.8	

The clinical features in our study in comparison to various ethnic groups are depicted in table -28. Our study had a greater prevalence of sclerosis as compared to study by

Reville et al and similar to the study in Thailand by Ruangjutipopan et al. and Iraq by Adhadh et al. Raynaud's phenomenon was lower in our population in comparison to western population, Iraq and Thailand. India has predominantly a tropical climate and extends 22° 00' N and 77° 00' E and hence has a higher temperature which probably contributes to the decreased prevalence of Raynaud's phenomenon in our study population. (100) Telangiectasia was lower in our studies as compared to the western population and Iraq and higher than the African Americans and Thais. This can be explained by the fact that telangiectasias could have been easier to view on a background of fair complexion with Fitzpatrick skin type 2 and 3 compared to our Fitzpatrick skin types 4 and 5. The commonest site was face in all the above mentioned studies.

Pigmentary alteration was commoner in our study(94%) as compared to other studies and much higher than the western population. Pigmentary alterations were also common among the African Americans and Iraqis. The types of pigmentary disturbance seen in these populations were not mentioned. The prevalence of digital ulcers and resorption in digits was lower in our study as compared to the western population. This can be explained by the lower incidence of Raynaud's phenomenon. The commonest site of flexion contracture was fingers involving the DIP joint in our study. To summarise pigmentatory disturbances was higher in our populations whereas Raynaud's phenomenon, digital ulcers and telangiectasia were less common than in western population. (78)(59)(72)

TABLE 28 - CLINICAL FEATURES IN VARIOUS ETHNIC GROUPS

Feature	Our study	Iraq (72)	Thailand (78)	American Whites (59)	American Hispanics (59)	African American (59)
No of patients	35	75	222	79	54	58
Skin Sclerosis	97.1	96.5	100	46	61	62
Raynaud's phenomenon	71.4	100	94.1	86	93	96
Telangiectasia	28.6	58	9.5	53	61	14
Pigmentary Disturbance	94.3	83	-	51	59	82
Hyperpigmentation	45.7	-	-	-	-	-
Salt and pepper pigmentation	65.7	-	-	-	-	-
Depigmentation	48.6	-	-	-	-	-
Gangrene	2.9	-	-	-	-	-
Flexion contracture	20	-	-	-	-	-
Digital ulcer	2.9	-	53.6	49	61	82
Resorption of digits	14.3	-	-	80	87	89

The systemic manifestations in our study in comparison with other studies both within India and outside India are shown in table -29. In our study the commonest systemic manifestation was pulmonary involvement and the commonest presentation being pulmonary fibrosis. The prevalence of pulmonary involvement (74.3%) in our study was mildly lower than the study by Pradhan et al. and higher than the study by Sharma et al and the western population. (12) (8) Gastrointestinal involvement in our study was comparable to the study by Sharma et al. and the western studies.(8) (59) The prevalence of GI involvement was surprisingly much lower in the study by Ruangjutipopan et al in Thailand and the study by Pradhan et al.(78)(12)The commonest presentation of gastrointestinal involvement was gastroesophageal reflux followed by oesophageal dysmotility. The prevalence of renal involvement in our study(3.1%) was lower than all the other studies. The prevalence of renal involvement was higher (25%) in the western population. (59)Cardiac involvement in our study was similar to the study by Pradhan et al. Musculoskeletal involvement in our study was lower as compared to the study by Pradhan et al.(12)

TABLE 29 - SYSTEMIC INVOLVEMENT

System	Our Study	Sharma et al (8)	Pradhan et al. (12)	Iraq (72)	American Whites (59)	American Hispanic (59)	African American (59)	Thailand (78)
No. of patients	35	75	110	75	79	54	78	222
Pulmonary	74.3	51.1	77.3	57.4	44.6	14	22	32
Renal	3.1	6	10.9	9	23	24	25	5.8
Cardiac	14.3	-	13.6	-	-	-	-	-
Gastro Intestinal	68.6	70.2	7.3	-	62	63	71	41.9
Musculo Skeletal	11.4	-	39.1	-	-	-	-	-

The nail fold dermoscopy findings in our study was compared with the findings in a study by Dogan et al. In our study, nail fold dermoscopy showing scleroderma pattern was seen in 77.1% of the patients. This was slightly lower than the study done by Dogan et al. The commonest nail fold capillary pattern was dilated capillaries in both the studies. The prevalence of dilated capillaries was 91.4% vs 49%. The commonest nail fold pattern in both diffuse and limited type of disease was dilated capillaries which was similar to the study by Dogan et al. In our study giant capillaries and avascular pattern were seen in one patient with the limited disease.

Scleroderma pattern was further divided into early, active and late pattern. (97)(96)(18) Early pattern was seen in 5 patients, active in 15 and late in 7 patients and non specific pattern was seen in 8 patients respectively. Active scleroderma pattern was the commonest pattern seen in association with systemic manifestation. None of the systemic manifestations showed a positive association with capillary patterns. This observation was similar to the observations by Dogan et al. In our study the commonest nail fold dermoscopy pattern seen with interstitial lung disease was active scleroderma pattern (52%) followed by late scleroderma pattern (20%). In our study, the patients with cardiac involvement the commonest patterns were active scleroderma pattern (40%) and late scleroderma pattern (40%). Patients with oesophageal reflux disease had active scleroderma pattern (46.7%) followed by non specific pattern (26.7%) and patients with oesophageal dysmotility had active scleroderma pattern (66.7%) followed by non specific pattern (22.2%).

The nail fold capillary changes noted in our study included capillary loop dilatation, drop outs, giant capillaries, capillary haemorrhage and avascular areas. In our study we noticed single abnormal finding in 7 patients, the commonest being dilated capillaries. Majority of our patients (n=11, 31.4 %) had 2 abnormal findings closely followed by 10 patients (28.6%) who had 3 abnormal nail fold findings. All five abnormal findings were seen in 2 patients. Hence, a combination of different dermoscopic findings can be seen in the same patient. Further studies will be

required to see if these dermoscopic patterns predict a particular systemic involvement.(90)

INVESTIGATIONS

Antinuclear antibody positivity was seen in 88.6% of our patients which was similar to the study by Sharma et al. (89.1%) and study by Pradhan et al.(85.5%). ANA positivity was similar to that in the western population. It was lower in the study by Adhadh et al.(67%). In our study the commonest type was speckled (35.5%) followed by speckled and nucleolar(25.8%). This was lower than the prevalence of speckled in the study by Sharma et al.(62.1%). The prevalence of both speckled and nucleolar was much higher in our study as compared to the study by Sharma et al. (25.8% vs 1.3%). Anti scl-70 was positive in 59.3% which was mildly lower than the study by Pradhan et al but higher than study by Sharma et al.(8)(12)

Interleukin -6 levels were elevated in 2 of the 7 patients tested with scl-70 positve diffuse systemic sclerosis. It has been noted in other studies that IL-6 is associated with increase in avascular areas in dermoscopy and a higher probability of digital ulcers. (37) Studies have shown a correlation of IL-6 levels with skin fibrosis. Further studies on serum IL-6 in systemic sclerosis will be required to establish relationship of IL-6 with dermoscopic patterns and skin fibrosis and its potential role as a therapeutic target.(35)(34)(39)

The commonest finding on CT thorax was ground glass opacities or NSIP (65.7%) which was higher in our study as compared the study by Sharma et al. (45%)

In our hospital based study, we tried to look at the cutaneous profile and nail fold dermoscopy of patients presenting to us with scleroderma. In our study, we had a female preponderance of patients with systemic sclerosis. The diffuse type of disease was commoner and was present in 91% of our study population. The mean duration of disease was higher in our study as compared to the previous studies. Upper limb was the commonest site of involvement with sclerodactyly being the commonest manifestation. Cutaneous sclerosis and pigmentation was higher in our study (97.1%). Raynaud's phenomenon, digital ulcers, gangrene and flexion contractures were less common in our study. The commonest systemic manifestation was interstitial lung disease. There was a significant association found between Rodnan skin score and interstitial lung disease. The commonest nail fold capillary abnormality was dilated capillaries seen in 91.4% of our study population. Scleroderma pattern was present in 77.1% of our study population with active pattern in 15 patients. Interleukin-6 was elevated in 2 of 7 patients tested. Nail fold dermoscopy is a useful tool for diagnosis, assessing disease severity and prognosis. Further studies are required to study the role of interleukin -6 in systemic sclerosis.

CONCLUSIONS

In our study of cutaneous profile and nail fold dermoscopy of patients with scleroderma, we observed the following findings:

1. There was a female preponderance in our study population with a male to female ratio of 1:6.

2. Mean duration of disease at presentation was 43.31$\pm$ 31.8 months.

3. There was a higher prevalence of diffuse type of disease(91%) in our study population.

4. Cutaneous sclerosis was present in 97.1% of our study population with the upper limb being the commonest site of involvement.

5. Pigmentary disturbances were commoner in our study(94.3%) as compared to the western population. The commonest pigmentary abnormality was salt and pepper pigmentation.

6. Prevalence of Raynaud's phenomenon was 71.4%.

7. The prevalence of digital ulcers(2.9%), gangrene(2.9%) and flexion contracture(20%) were lower in our study.

8. Prevalence of telangiectasia (26.8%) and calcinosis(8.65%) was lower in our study.

9. Neck sign was seen in 57.1% of patients.

10. Round finger pad sign and pterygium inversum unguis was seen in 25.7% and 17.1% patients respectively.

11. The commonest systemic manifestation was interstitial lung disease (74.3%) followed by gastrointestinal involvement (68.6%).

12. The prevalence of renal involvement(3.1%) was lower in our study.

13. The commonest pattern in nail fold dermoscopy was dilated capillaries seen in 91.4% of our patients.

14. In nail fold dermoscopy scleroderma pattern was seen in 77.1% of our patients, 5 patients with early pattern, 15 with active pattern and 7 with late pattern.

15. More than one abnormal dermoscopic finding was seen in 80 % of our study population. Presence of two abnormal findings was the commonest pattern seen in 11 patients.

16. There was no statistically significant association between nail fold dermoscopy patterns with systemic manifestations.

17. Early, active and late pattern of capillary pattern were associated with increasing trend of disease duration but this was not of statistical significance.

18. Modified Rodnan skin score showed statistically significant positive association with interstitial lung disease($p=0.026$).

19. Interleukin-6 was performed in a subset of scl-70 antibody diffuse systemic sclerosis and it was elevated in 2 of 7 patients.

LIMITATIONS

1) The sample size was inadequate to delineate the association of nail fold dermoscopic findings with the type of disease and systemic manifestations.
2) Mean value of megacapillaries and capillary density was not measured in our study.
3) Interleukin -6 could be performed only on a subset of patients, hence a larger study will be required to correlate serum interleukin -6 levels with skin severity scores.

RECOMMENDATIONS

1. A baseline dermoscopy should be performed for all patients with suspected systemic sclerosis to predict the course of the disease as early initiation of therapy can prevent complications

2. Further studies are required to study nail fold capillary abnormalities in our setting and also its association with systemic manifestations

3. Video morphometry studies are required to study capillary architecture and inter capillary distance

4. Further studies and follow up are required to study the role of interleukin -6 levels in fibrosis in systemic sclerosis and its response with treatment

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ANNEXURE –I

AMERICAN COLLEGE OF RHEUMATOLOGY(ACR) CRITERIA

Major criteria

Symmetric proximal sclerosis extending beyond metacarpal phalangeal joint and metatarsal joint

Minor criteria

1) sclerodactyly

2) digital pitted scars/loss of substance over finger pads

3) bibasilar fibrosis

ANNEXURE -II

Patient Information Sheet and consent forms

Study Title:

Cutaneous Profile and nail fold dermatoscopy of scleroderma patient

Purpose of research:

Scleroderma is a disease for which the exact aetiology of which is not known. Scleroderma predominantly affects the skin causing tightening. It can also affect the lungs, heart, gastro intestinal system and blood vessels. In this study I intend to study the various skin manifestations associated with the disease . Also a particular substance secreted by the white blood cells in our body known as Interleukin 6 (IL-6) is known to be associated with the skin lesions in scleroderma. I further intend to view the capillaries in the skin around the nails using a dermatoscope. This gives a magnified image of the capillaries and helps to predict stage of the disease.

Expected duration of the Subject's participation:

Only at the time of presentation of the patient at the Dermatology Unit - II OPD/ Rheumatology OPD/ in-patients with scleroderma. Patient will be adviced to come for follow up after 3 months during which time a blood test will be done.

Description of the procedures:

This study would involve recording of the patient's relevant details and detailed examination of skin lesions. A dermatoscopy will be performed to view the capillaries around the finger nails. In selected patients(patients with extensive skin involvement) a blood sample will be collected for measurement of interleukin 6. Clinical photographs of the skin lesions may be taken.

Risks or discomforts to the Subject:

As the study does not include any trial treatment, there is no additional risk for the patient due to participation in study. The patient will not incur any additional cost by taking part in the study.

Benefits to the Subject:

It may help in further management of the condition.

Benefits to others:

Information gathered from this study might help in the understanding of the cutaneous aspects of scleroderma. An understanding of the role of IL 6 and nail fold dermatoscopy may help in future contribute to exploration of potential treatment options as well as prognosis of scleroderma.

Confidentiality:

Only the investigators of this study will be able to access the patient's medical records. Patient's identity will not be revealed in any form or released to third parties or published.

Participation:

The patient's participation in the study entirely voluntary and the patient is free to withdraw from the study at any time, without stating any particular reason. Refusal to participate or withdrawal from the study will not involve any penalty or loss of benefits to which the patient is otherwise entitled.

Approximate number of Subjects enrolled in the study – 100

Contact person:Dr Priya Sara Kuryan, PG registrar, Department of Dermatology, leprosy and Venerology Unit II, CMC, Vellore

Phone – 04162282054

email – derm@cmcvellore.ac.in

ANNEXURE – III

Cutaneous Profile and nail fold dermatoscopy of scleroderma patients and serum interleukin 6 levels correlation with modified Rodnan skin severity score

Proforma

Date _____ Sl.no

Name _____ CMCH no. _____ Age _____ Sex ____

Address
Contact no

Type of disease: Diffuse/Limited Duration of disease _____months

Duration of Raynaud's phenomenon _____ months Duration of sclerosis _____ months

Past History of skin lesions Yes/ No If yes, details _____

Duration of treatment _____ months

Treatment details

Drug	Dose	Duration
Topical		
Systemic		
Steroids		
Mycophenolate mofitel		
Azathioprine		
Cyclophosphamide		
Hydroxychloroquine		
Others		

Skin lesions	Present/Absent
Face	
Radial furrows	
Beaked nose	
Inability to evert lower eyelid	
Smoothening of forehead Expression	
Mouth opening	mm
Mask like facies	
Peri-orbital Edema	
Hand	
Digital ulcers	
Digital pitted scars	
Pitting edema of fingers	
Round finger pad sign	
Flexion contractures	
Sclerodactyly	
Gangrene	
Dystrophic nails	
Ragged cuticles	
Resorption of phalanges	
Pterygium inversium unguis	
Cobble stone appearance	
Leg	
Leg ulcers	
Livedo reticularis	
Atrophie blanche	
Gangrene	
Raynaud's phenomenon	
Neck sign	
Others	

Skin lesions	Present/Absent if present site
Sclerosis	
Calcinosis	
Telangiectasia	
Hyper pigmentation	
Salt and pepper pigmentation	
Hypopigmentation	

Nail fold Dermatoscopy

Right hand

Findings	Thumb	Index finger	Middle finger	Ring finger	Little finger
Normal capillary configuration					
Dilated capillary loops					
Giant capillaries					
Capillary haemmorhage					
Avascular area					
Drop out					

Left hand

Findings	Thumb	Index finger	Middle finger	Ring finger	Little finger
Normal capillary configuration					
Dilated capillary loops					
Giant capillaries					
Capillary haemmorhage					
Avascular area					
Drop out					

Systemic manifestations

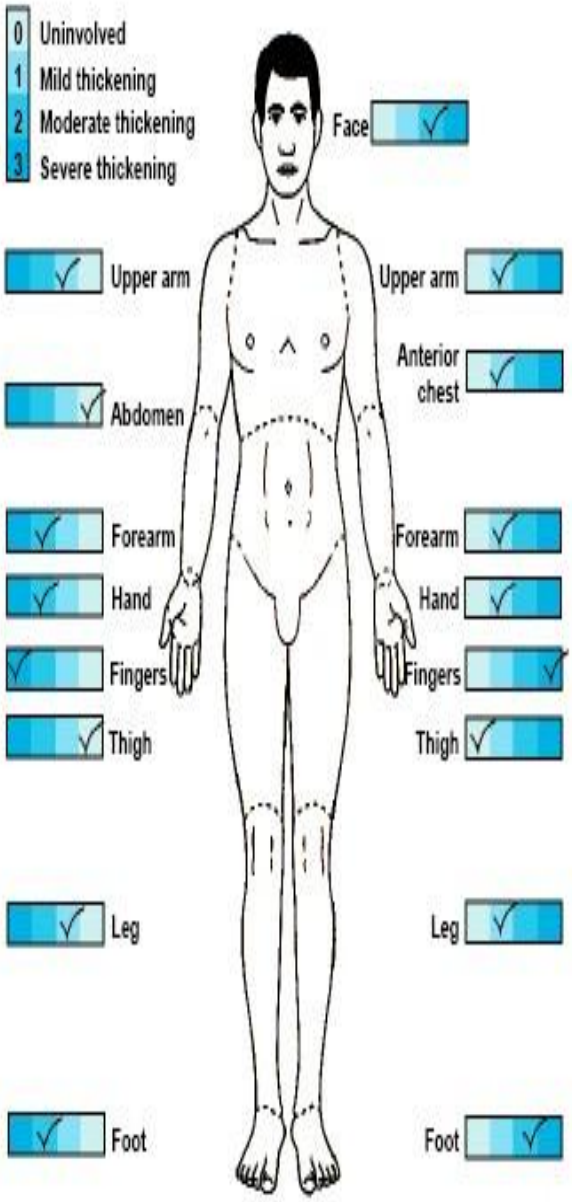
Systemic signs	Present/absent
GI	
Oesophageal dysmotility	
Oesophageal reflux	
Others	
Respiratory	
Interstitial lung disease	
Pulmonary artery hypertension	
Cardiac	
Renal	
Muscles	
Others	

Investigations

Investigation	Result
ANA	
Anti- centromere antibody	
Anti – topo isomerase antibody	
Anti RNP antibody	
Echo	
HRCT chest	

Date		
Serum interleukin-6		
Rodnan's skin skin score		

Skin sclerosis score



Modified Rodnan Skin score

Face	3	
Neck	3	
Anterior chest	3	
Abdomen	3	
Back - upper	3	
Back - lower	3	
	9 (18)	
Upper arm	3	3
Forearm	3	3
Hand	3	3
Fingers	3	3
Thigh	3	3
Leg	3	3
Foot	3	3
	21	21
Maximum (17 site)		51
20 site		60

UniqueKey	serialno	cmcno	age	sex	TYPEOFDISEASE	DURATIONOFDISEASEINMONTHS	DURRAYNAUDS
1	35	898478	52	FEMALE	DIFFUSE	24	6
2	34	842145	31	FEMALE	DIFFUSE	24	24
3	33	143885	17	FEMALE	DIFFUSE	24	20
4	32	895460	33	MALE	DIFFUSE	6	0
5	31	172041	36	FEMALE	DIFFUSE	96	60
6	30	62462	49	FEMALE	DIFFUSE	72	60
7	29	790621	31	FEMALE	DIFFUSE	9	9
8	28	983059	39	FEMALE	DIFFUSE	48	36
9	27	56748	26	FEMALE	LIMITED	30	0
10	26	798049	29	FEMALE	DIFFUSE	24	24
11	25	729888	37	FEMALE	DIFFUSE	60	0
12	24	993776	29	FEMALE	DIFFUSE	36	0
13	23	18099	36	FEMALE	DIFFUSE	12	3
14	22	743938	21	MALE	DIFFUSE	12	12
15	21	417859	24	MALE	DIFFUSE	29	29
16	20	747687	27	FEMALE	DIFFUSE	4	6
17	19	778021	48	MALE	DIFFUSE	120	0
18	18	494627	50	FEMALE	DIFFUSE	22	22
19	17	612549	56	FEMALE	DIFFUSE	36	0
20	16	888727	44	MALE	DIFFUSE	120	60
21	15	766436	52	FEMALE	DIFFUSE	60	50
22	14	70578	20	FEMALE	DIFFUSE	12	12
23	13	389974	43	FEMALE	DIFFUSE	72	72
24	12	716214	34	FEMALE	DIFFUSE	72	72
25	11	6445	43	FEMALE	LIMITED	60	0
26	10	161638	20	FEMALE	DIFFUSE	60	0
27	9	567629	38	FEMALE	DIFFUSE	48	0
28	8	65452	22	FEMALE	DIFFUSE	6	0
29	7	29181	28	FEMALE	DIFFUSE	18	18
30	6	149926	36	FEMALE	DIFFUSE	66	60
31	5	96878	36	FEMALE	DIFFUSE	60	48
32	4	129126	53	FEMALE	LIMITED	24	18
33	3	1347235	25	FEMALE	DIFFUSE	18	12
34	2	206143	62	FEMALE	DIFFUSE	36	36
35	1	572791	43	FEMALE	DIFFUSE	96	72

DURSCLEROSIS	PASTHISTORYOFSKINLESIONS	DURATIONOFTREATMENT	RADIALFURROWS	BEAKEDNOSE
24	No	7	Yes	Yes
24	No	0	Yes	Yes
24	No	6	Yes	Yes
6	No	3	Yes	Yes
96	No	2	No	No
72	No	6	Yes	Yes
8	No		No	Yes
48	No	36	No	No
0	No	0	No	No
12	No	6	No	Yes
0	No	36	Yes	Yes
0	No		Yes	Yes
3	No	10	Yes	Yes
12	No	2	Yes	Yes
29	No	24	Yes	Yes
0	No	0	No	No
120	No	12	Yes	Yes
20	No	13	Yes	Yes
36	No	24	Yes	Yes
120	No	2	No	No
60	No	48	Yes	Yes
12	No	8	No	No
72	No	0	Yes	Yes
72	No	6	Yes	Yes
6	No	0	Yes	Yes
60	No	0	Yes	Yes
48	No	36	Yes	Yes
6	No	0	Yes	Yes
18	No	1	Yes	Yes
66	No	36	Yes	Yes
60	No	0	Yes	Yes
24	No	18	No	No
18	No	2	No	No
36	No	0	Yes	Yes
96	No	48	Yes	Yes

INABILITTYTOEVERTLOWEREYELID	SMOOTHENINGOFFOREHEADEXPRESSION	MOUTHOPENINGINMM
No	No	20
Yes	Yes	20
Yes	Yes	30
Yes	Yes	30
No	No	30
Yes	Yes	30
Yes	Yes	30
Yes	No	32
No	No	32
Yes	Yes	35
Yes	Yes	35
Yes	No	38
Yes	Yes	40
Yes	No	40
Yes	Yes	40
No	No	40
Yes	Yes	42
No	No	46
No	No	50
Yes	Yes	50
Yes	No	50
No	No	50
Yes	Yes	50
Yes	Yes	52
No	No	56
No	No	60
Yes	Yes	60
Yes	No	60
Yes	Yes	60
Yes	No	60
Yes	Yes	60
Yes	No	63
No	No	64
Yes	Yes	64
Yes	Yes	20

MASKLIKEFACIES	PERIORBITALEDEMA	DIGITALULCERS	DIGITALPITTEDSCARS	PITTINGEDEMAOFFINGERS
No	No	No	Yes	No
Yes	No	No	Yes	No
Yes	No	No	Yes	No
No	No	No	No	No
No	No	No	No	No
Yes	No	No	Yes	No
Yes	No	No	Yes	No
No	No	No	Yes	No
No	No	No	No	No
No	No	Yes	Yes	No
Yes	No	No	Yes	No
No	No	No	No	Yes
Yes	No	No	Yes	No
No	No	No	Yes	No
Yes	No	No	Yes	No
No	No	No	No	Yes
Yes	No	No	Yes	No
Yes	Yes	No	Yes	No
No	No	No	No	No
No	No	No	No	No
No	No	No	Yes	No
No	No	No	Yes	No
No	No	No	No	No
No	No	No	Yes	No
No	No	No	No	No
No	No	No	No	No
Yes	No	No	No	No
No	No	No	No	No
Yes	No	No	No	No
Yes	No	No	No	No
Yes	No	No	Yes	No
No	No	No	No	No
No	No	No	Yes	No
Yes	No	No	No	No
No	No	No	No	No

state	ROUNDFINGERPADSIGN	FLEXIONCONTRACTURES	SCLERODACTYLY	GANGRENE
sikkim	Yes	No	Yes	No
west bengal	No	No	Yes	No
tamilnadu	No	Yes	Yes	No
ap	No	No	Yes	No
bangladesh	No	No	Yes	Yes
jharkhand	No	No	Yes	No
west bengal	No	Yes	Yes	No
jharkhand	Yes	No	Yes	No
kerala	No	No	Yes	No
assam	No	No	Yes	No
west bengal	Yes	Yes	No	No
tamilnadu	Yes	No	Yes	No
kerala	Yes	No	Yes	No
west bengal	No	No	No	No
west bengal	Yes	Yes	Yes	No
west bengal	No	No	Yes	No
jharkand	Yes	No	Yes	No
west bengal	Yes	No	Yes	No
tamilnadu	No	No	Yes	No
ap	Yes	No	Yes	No
west bengal	No	No	No	No
jharkhand	Yes	No	Yes	No
tamilnadu	No	No	Yes	No
west bengal	Yes	Yes	No	No
ap	No	No	No	No
jharkhand	No	Yes	Yes	No
chandigarh	No	No	Yes	No
tamilnadu	No	No	Yes	No
west bengal	No	No	Yes	No
west bengal	No	No	Yes	No
west bengal	No	No	Yes	No
tamilnadu	No	No	Yes	No
bangladesh	No	No	Yes	No
west bengal	No	No	Yes	No
west bengal	No	Yes	Yes	No

DYSTROPHICNAILS	RAGGEDCUTICLES	RESORPTIONOFPHALANGES	PTERYGIUMINVERSUMUNGUIS
No	No	No	No
No	Yes	No	Yes
No	Yes	No	No
No	No	No	No
No	No	No	No
No	Yes	No	No
Yes	Yes	No	No
No	Yes	No	Yes
No	No	No	No
No	Yes	Yes	Yes
No	Yes	Yes	No
No	Yes	No	Yes
Yes	Yes	No	No
No	Yes	No	No
No	Yes	Yes	Yes
No	No	No	No
No	Yes	Yes	No
No	Yes	No	No
No	No	No	No
No	Yes	Yes	No
No	No	No	No
No	No	No	No
No	Yes	No	No
Yes	No	No	No
No	Yes	No	No
No	No	No	No
No	Yes	No	No
No	Yes	No	No
Yes	Yes	No	No
No	Yes	No	No
No	Yes	No	Yes
No	No	No	No
No	Yes	No	No
No	Yes	No	No
No	No	No	No

COBBLESTONEAPPEARANCE	LEGULCERS	LIVEDORETICULARIS	ATROPHIEBLANCHE	GANGRENE1
No	No	No	No	No
No	No	No	No	No
No	No	No	No	No
No	No	No	No	No
No	No	No	No	No
No	No	No	No	No
No	No	No	No	No
No	Yes	No	Yes	No
No	No	No	No	No
No	No	No	No	No
No	No	No	No	No
No	No	No	No	No
Yes	No	No	No	No
No	No	No	No	No
No	No	No	No	No
No	No	No	No	No
No	No	No	No	No
No	No	No	No	No
No	No	No	No	No
No	Yes	No	No	No
No	No	No	No	No
No	No	No	No	No
No	No	No	No	No
No	No	No	No	No
No	No	No	No	No
No	Yes	No	No	No
No	No	No	No	No
No	No	No	No	No
No	No	No	No	No
No	No	No	No	No
No	No	No	No	No
No	No	No	No	No
No	No	No	No	No
No	No	No	No	No
No	No	No	No	No

RAYNAUDSPHENOMENON	NECKSIGN	OTHERS	ifyessite	ifyessitecont	ifyessitegangrene	sclerosis	site1
No	No	No				Yes	face
Yes	Yes	Yes				Yes	face
Yes	Yes	No		elbow		Yes	face
No	Yes	No				Yes	upper limb
Yes	No	Yes			index, middle R	Yes	chest
Yes	Yes	No				Yes	face
No	Yes	No		R hand		Yes	face
No	Yes	No	R ring			Yes	face
No	No	No				Yes	upper limb
Yes	Yes	No				Yes	face
No	No	No	ring R	L little		Yes	upper limb
Yes	Yes	No	ring R			Yes	face
No	Yes	No	index			Yes	face
Yes	Yes	Yes				Yes	face
Yes	Yes	No				Yes	upper limb
No	No	No				Yes	upper limb
No	No	No				Yes	upper limb
Yes	No	Yes	middle L			Yes	upper limb
No	Yes	No				Yes	abdomen
No	Yes	No	R ring			Yes	face
No	Yes	No				No	
No	Yes	Yes	index R			Yes	face
Yes	Yes	No				Yes	face
Yes	No	No				Yes	upper limb
No	No	No				Yes	upper limb
No	Yes	No		hands		Yes	face
No	No	No				Yes	upper limb
No	No	No				Yes	face
No	No	No				Yes	upper limb
No	No	Yes				Yes	upper limb
No	Yes	Yes				Yes	upper limb
No	No	No				Yes	upper limb
No	Yes	No				Yes	face
No	No	No				Yes	upper limb
No	Yes	No		finger		Yes	upper limb

site2	site3	site4	calcinosis	sitecalcinosis	telangiectasia	ifyessitetelangectasia
chest	abdomen	upper limb	No		No	
upper limb	lower limb		No		Yes	R cheek
upper limb	lower limb		No		No	
lower limb			No		No	
abdomen	upper limb	lower limb	No		Yes	cheek
chest	upper limb	lower limb	No		No	
upper limb	lower limb	chest	No		No	
upper limb	lower limb		No		Yes	cheek
			No		No	
upper limb			No		No	
lower limb			No		No	
upper limb			No		No	
upper limb	lower limb		No		No	
upper limb			No		No	
lower limb			No		No	
			No		Yes	R cheek
lower limb	chest	back	No		Yes	face,cheek
lower limb			Yes		Yes	cheek
upper limb	lower limb		No		No	
upper limb	lower limb		Yes		Yes	r cheek
			No		No	
chest	upper limb	lower limb	No		No	
upper limb			No		No	
lower limb			No		No	
			No		No	cheek
upper limb	lower limb		No		No	
			No		Yes	cheek and palm
chest	upper limb	abdomen	No		No	
			No		No	
			No		No	
			No		No	
lower limb	face		No		No	
upper limb	lower limb	back	No		Yes	cheeks
			No		No	
face	chest		Yes	knuckle	Yes	cheeks

hyperpigmentation	ifyessitehyperpigmentation	saltandpepperpigmentation
No		No
Yes	trunk,UL,LL	Yes
No		Yes
Yes	face, neck,UL	Yes
Yes	UL,LL	Yes
No		No
No		Yes
Yes	face,trunk,UL	Yes
Yes	generalised	Yes
Yes	face,ear,neck,hands	Yes
Yes	UL,LL	Yes
No		No
No		Yes
Yes	arms	Yes
Yes	FACE	Yes
Yes	forearm	No
Yes	diffuse	Yes
No		Yes
No		Yes
No		Yes
No		No
Yes	dorsum if hand	Yes
No		No
Yes	face,chest	No
Yes	face,UL	No
Yes	trunk UL LL	No
No		No
No		Yes
Yes	generalised	No
No		Yes
No		Yes
No		Yes
No		Yes
No		Yes
No		No

ifyessaltandpeppper	hypopigmentation	ifyessitehypopigmentation
	Yes	eyebrow, nose, external ear, periorbital
scalp	Yes	trunk,UL,LL
earlobe,neck,UL,scalp	No	
retroauricular,occiputal,napeof neck	Yes	pinna,fingers
back,neck	Yes	hand,feet
	No	
wrist	No	
scalp,neck,back	Yes	LL
back,arm,hands	No	
back,retroauricular	Yes	L eyelid
chest,abdo,knee	No	
	Yes	ear,neck
face,chest,hand	Yes	bacl
CHEST,BACK,l ARM	Yes	L eyelid, perioral
face,back,trunk	No	
	No	
face neck UL	No	
chest,back,scalp	Yes	right fingers
forehead,neck,scalp,UL	No	
chest	No	
	Yes	back,neck
forearm	Yes	face
	Yes	neck,chest
	No	
	No	
	Yes	face
	No	
chest ll	No	
	No	
back	Yes	neck chest
retroauricular hair line	No	
back	Yes	waist
face neck	No	
forehead chest forearm shin	No	
	Yes	dorsa of hand

othersspecify	normalcapillaryconfigurationthumb	normalcapillaryconfigurationindex
	No	No
melasma	No	No
	No	No
	No	No
tinea corporis	No	No
	No	No
	No	No
	No	No
	No	No
	Yes	No
	Yes	No
	No	No
	No	No
	Yes	No
	No	No
	No	Yes
	No	No
	Yes	No
	No	No
	No	No
	Yes	Yes
	Yes	Yes
	Yes	Yes
	No	No
	Yes	No
	No	No
	No	No
	No	No
	No	No
melanonychia	Yes	No
scarring alopecia	No	No
	Yes	Yes
	No	No
	No	No
	No	No

normalcapillaryconfigurationring	normalcapillaryconfigurationlittle	dilatedcapillaryloopsthumb
No	No	Yes
No	No	No
No	No	Yes
No	No	No
No	No	No
No	No	Yes
No	No	Yes
No	No	Yes
No	No	Yes
No	No	Yes
No	Yes	No
No	No	No
No	No	Yes
No	Yes	No
No	Yes	No
Yes	Yes	No
No	No	No
No	No	Yes
Yes	No	Yes
No	No	No
No	No	No
No	No	No
No	No	No
No	No	No
Yes	Yes	No
No	No	Yes
No	No	Yes
No	No	Yes
No	No	Yes
Yes	Yes	No
No	No	Yes
No	No	No
No	No	No
No	No	No
No	No	Yes

dilatedcapilllaryloopsindex	dilatedcapillaryloopsmiddle	dilatedcapillaryloopslittle	giantcapillariesthumb
Yes	No	No	No
Yes	Yes	No	No
No	No	Yes	No
No	No	No	No
No	Yes	No	No
No	Yes	Yes	No
Yes	No	No	No
Yes	No	No	No
Yes	No	No	No
No	Yes	No	No
No	Yes	No	No
Yes	Yes	No	No
Yes	No	No	No
Yes	Yes	No	No
No	No	No	No
No	No	No	No
Yes	Yes	No	No
Yes	Yes	No	No
No	No	No	No
No	Yes	No	No
Yes	Yes	No	No
No	No	No	No
No	Yes	No	No
Yes	No	No	No
Yes	No	No	No
Yes	No	No	No
Yes	No	No	No
Yes	No	Yes	No
Yes	No	No	No
Yes	Yes	No	No
Yes	No	No	No
Yes	Yes	No	No
No	Yes	Yes	No
No	Yes	No	Yes
Yes	No	No	Yes

dilatedcapillariesring	giantcapillariesindex	giantcapillariesmiddle	giantcapillariesring	giantcapillarieslittle
No	No	Yes	No	No
No	No	No	No	No
No	No	No	No	No
No	No	No	No	No
Yes	No	No	No	No
Yes	No	No	No	No
No	No	No	No	No
No	No	No	Yes	No
No	No	Yes	No	No
No	No	Yes	No	No
No	No	No	Yes	No
No	No	No	No	No
No	No	Yes	Yes	No
No	No	No	No	No
No	No	No	No	No
No	No	No	No	No
No	No	No	No	No
No	No	No	Yes	No
No	No	No	No	No
No	No	No	No	No
Yes	No	No	No	No
No	No	No	No	No
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No	No	No	No	No
No	No	No	No	No
No	No	No	No	No
No	No	No	No	No
No	No	No	No	No
Yes	Yes	No	No	No
No	No	No	No	No
No	No	No	No	No
No	No	No	No	No
No	No	No	No	No
Yes	No	No	No	No
Yes	No	No	No	No
No	No	No	No	No

capillaryhaemmmmorhagethumb	capillaryhaemmorhageindex	capillaryhaemmorhagemiddle
No	No	No
No	No	No
No	No	No
No	No	No
No	No	No
No	Yes	Yes
No	No	Yes
No	Yes	Yes
Yes	Yes	No
Yes	No	No
No	No	No
No	No	No
No	No	No
No	Yes	Yes
No	No	No
No	No	No
No	No	Yes
No	No	Yes
Yes	No	No
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No	No	No
No	No	No
No	No	No
No	No	No
No	No	No
No	No	Yes
No	Yes	Yes
No	No	No
No	No	No
No	No	Yes
No	Yes	Yes
No	No	No
No	No	No
No	No	No
No	Yes	No

capillaryhaemmmorhagering	capillaryhaemmorhagelitttle	Avascularareathumb	avascularareaindex
No	No	No	No
No	No	No	No
No	No	No	No
No	No	No	No
No	No	No	No
No	No	No	No
Yes	No	No	No
No	No	No	No
Yes	Yes	No	No
Yes	No	No	No
No	No	No	Yes
No	No	No	No
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No	No	No	No
No	No	No	No
No	No	No	No
No	No	No	No
No	No	No	No
Yes	Yes	No	No
No	No	No	No
No	No	No	No
No	No	No	No
No	Missing	No	No

avascularareamiddle	avascularearing	avascularearealittle	othersright	othersrightindex	othersrightmiddle
No	No	No	No	No	No
No	No	No	No	No	No
No	No	No	No	No	Yes
No	No	No	Yes	No	No
No	No	No	No	No	No
No	No	No	No	Yes	Yes
No	No	Yes	Yes	Yes	No
No	No	No	No	No	No
No	No	No	No	No	No
No	No	No	No	Yes	Yes
Yes	No	No	No	No	No
No	No	No	No	No	No
No	No	No	No	No	No
No	No	No	Yes	Yes	No
No	Yes	No	No	No	No
No	No	No	No	No	Yes
No	No	No	No	No	No
No	No	No	No	No	No
No	No	No	No	No	No
No	No	No	No	No	No
No	No	No	No	Yes	Yes
No	No	No	No	No	Yes
No	No	No	No	No	No
No	No	No	No	Yes	No
No	No	No	No	No	No
No	No	No	No	No	No
Yes	No	No	No	Yes	Yes
No	No	No	No	Yes	Yes
No	No	No	No	No	Yes
No	No	No	No	Yes	No
No	No	No	Yes	Yes	No
No	No	No	No	No	No
No	No	No	Yes	Yes	Yes
No	No	No	No	No	Yes
Yes	Yes	Yes	No	No	No

othersrightring	othersrightlittle	normalcapilllaryconfigurationthumbleft	normalcapillaryconfigurationindex1
No	No	No	No
Yes	Yes	No	No
Yes	No	No	No
No	Yes	Yes	No
No	No	No	No
No	No	No	No
No	No	No	No
No	No	No	No
No	No	No	No
No	No	No	Yes
No	No	Yes	No
No	No	No	No
No	No	No	No
Yes	Yes	No	No
Yes	No	No	No
No	No	No	No
No	No	No	No
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Yes	No	No	No
Yes	No	No	Yes
Yes	No	No	No
No	No	Yes	Yes
No	No	No	No
No	Yes	No	No
Yes	No	No	No
Yes	No	No	No
No	No	Yes	Yes
No	No	No	No
No	No	Yes	No
No	No	No	No
Yes	No	No	No
No	No	No	No

normalcapillaryconfigurationmiddlelt	normalcapillaryconfigurationringlt	normalcapillaryconfigurationlittle1
No	No	No
No	No	No
No	No	No
Yes	Yes	No
No	No	No
No	No	No
No	No	No
No	No	No
No	No	No
No	No	Yes
No	No	No
No	No	No
No	No	No
No	Yes	No
No	No	Yes
No	Yes	Yes
No	No	No
No	No	No
No	No	No
No	No	No
No	No	No
No	No	No
Yes	No	No
No	No	No
Yes	Yes	Yes
No	No	No
No	No	No
No	No	No
No	No	No
No	No	No
No	No	No
No	No	No
No	No	No
No	No	No
No	No	No

dilatedcapillaryloops	dilatedcapillaryloopsindexlt	dilatedcapilllaryloosmiddlelt	dilatedcapillaryloopsringlt
Yes	Yes	No	No
Yes	Yes	No	No
No	No	No	No
No	No	No	No
Yes	Yes	No	No
Yes	Yes	No	Yes
Yes	No	No	Yes
No	Yes	Yes	No
Yes	Yes	No	No
No	Yes	Yes	Yes
No	Yes	No	Yes
No	No	Yes	Yes
Yes	Yes	No	No
Yes	Yes	Yes	Yes
No	No	No	No
No	No	No	No
No	Yes	Yes	No
No	No	No	No
Yes	Yes	Yes	No
No	Yes	Yes	No
No	No	No	No
Yes	Yes	No	No
Yes	No	No	No
Yes	Yes	No	No
No	No	No	No
No	No	No	No
Yes	Yes	No	No
Yes	Yes	No	No
Yes	Yes	No	No
No	No	Yes	Yes
No	Yes	Yes	Yes
No	Yes	Yes	No
No	Yes	Yes	No
Yes	Yes	No	No
Yes	Yes	No	No

dilatedcapillaryloopslittlelt	giantcapillariesthumbleft	giantcapillariesindexlt	giantcapillariesmiddlelt
No	No	No	Yes
No	No	No	No
No	No	No	No
No	No	No	No
No	No	No	No
Yes	No	No	No
No	No	No	No
Yes	No	No	No
Yes	No	No	No
Yes	Yes	No	No
Yes	No	No	No
No	No	No	No
No	No	No	Yes
Yes	No	No	No
No	No	No	No
No	No	No	No
No	No	Yes	Yes
No	No	No	No
No	Yes	Yes	Yes
No	No	No	No
No	No	Yes	No
No	Yes	Yes	Yes
No	No	No	No
No	No	No	No
No	No	No	No
No	No	No	No
No	Missing	No	No
No	No	No	No
No	No	No	No
Yes	No	No	No
No	No	No	No
No	No	No	No
No	No	No	No
Yes	No	No	No
No	No	No	No

giantcapillariesringlt	giantcapillarieslittlelt	normalcapillaryconfigurationmiddle1
Yes	No	No
No	No	No
No	No	No
No	No	No
No	No	No
No	No	No
No	No	No
Yes	No	No
No	No	No
No	Yes	No
No	No	No
No	No	No
No	No	No
No	No	No
No	No	Yes
No	No	No
No	No	No
No	No	No
Yes	Yes	No
No	No	No
No	No	No
Yes	Yes	No
No	No	No
No	No	No
No	No	Yes
No	No	No
No	No	No
No	No	No
Yes	No	No
No	No	No
No	No	No
No	No	No
No	No	No
No	No	No

capillaryhaemmorhagethumblt	capillaryhaemmmorhageindexlt	capillaryhaemmorhagemiddlelt
No	No	No
No	No	No
No	No	No
No	No	No
No	No	No
No	No	Yes
Yes	Yes	No
No	No	Yes
No	Yes	Yes
No	No	No
No	No	No
No	No	No
No	No	No
No	No	No
No	No	No
No	No	No
No	No	No
No	No	Yes
No	No	No
No	No	No
Yes	No	No
No	No	No
No	No	No
No	No	No
No	Yes	Yes
No	No	Yes
No	Yes	Yes
No	No	No
Yes	Yes	Yes
Yes	Yes	No
No	No	No
No	No	No
No	No	No
Yes	Yes	Yes

capillaryhaemmorhageringlt	capiilaryhaemmorhagelitttlelt	avasculatltthumb	avasculatltindex
No	No	No	No
No	No	No	Yes
No	No	No	No
No	No	No	No
No	No	No	No
Yes	No	No	No
No	No	No	No
No	No	No	No
Yes	No	No	No
Yes	Yes	No	No
No	No	No	No
No	No	No	No
No	No	No	No
Yes	No	Yes	Yes
No	No	No	No
No	No	No	No
Yes	No	No	No
Yes	No	No	No
No	No	No	No
No	No	No	No
No	No	No	No
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No	No	No	No
No	No	No	No
No	No	No	No
Yes	No	No	No
No	No	No	No
No	No	No	No
No	No	No	No
No	No	No	No
No	No	No	No
No	No	No	No
Missing	No	No	No
No	No	No	No

avascularltmiddle	avascularltring	avascularltlittle	othersltthumb	othersltindex	othersltmiddle	othersltring
No	No	No	No	No	No	No
No	No	No	No	No	No	Yes
No	No	No	No	Yes	Yes	Yes
No	No	No	No	Yes	Yes	No
No	No	No	No	No	No	No
No	No	No	No	Yes	Yes	No
No	No	No	No	No	Yes	No
No	No	No	No	No	No	No
No	No	No	No	No	No	No
Yes	No	No	Yes	No	No	No
Yes	No	No	No	No	No	No
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No	No	No	No	No	No	No
Yes	Yes	Yes	No	No	Yes	Yes
No	Yes	No	No	No	No	No
No	No	No	No	No	No	No
No	No	No	No	No	No	No
Yes	Yes	No	No	Yes	No	No
No	No	No	No	Yes	Yes	No
No	No	No	No	No	No	No
No	No	No	No	No	Yes	Yes
No	No	No	No	Yes	Yes	No
No	No	No	No	Yes	No	Yes
No	No	No	No	No	Yes	No
No	No	No	No	No	No	No
No	Yes	Yes	No	No	No	No
No	No	No	Yes	No	Yes	Yes
No	No	Yes	No	Yes	Yes	Yes
No	No	No	No	No	Yes	Yes
No	No	No	No	No	No	Yes
No	No	No	No	Yes	Yes	Yes
No	No	No	No	No	No	No
No	No	No	No	Yes	Yes	No
No	No	No	No	Yes	Yes	No
No	Yes	Yes	No	No	No	No

othersltlittle	oesoophagealdysmotility	oesophagealreflux	othersgi	interstitiallungdisease
No	No	No	Missing	Yes
Yes	No	Yes	No	Yes
No	No	Yes	No	Yes
No	No	Yes	No	Yes
No	Yes	No	No	No
No	No	No	No	Yes
No	No	No	No	Yes
No	No	No	No	Yes
No	No	No	No	No
No	Yes	Yes	No	Yes
No	No	No	No	Yes
No	No	Yes	No	Yes
No	No	No	No	Yes
Yes	Yes	Yes	No	Yes
No	No	No	No	No
No	No	Yes	No	No
No	Yes	Yes	No	No
Yes	No	Yes	No	Yes
No	No	Yes	No	Yes
No	Yes	Yes	No	Yes
Yes	Yes	No	No	Yes
No	No	No	No	Yes
No	Yes	No	No	Yes
No	No	No	No	No
No	No	No	No	No
No	No	Yes	No	No
Yes	No	No	No	Yes
Yes	No	No	No	Yes
Yes	No	Yes	No	No
No	No	Yes	No	Yes
No	Yes	Yes	No	Yes
No	No	No	No	No
No	No	No	No	Yes
Yes	Yes	No	No	Yes
No	No	No	No	Yes

pulmonaryarteryhypertension	cardiac	renal	muscles	otherssystemic	anaresult	echo	sel70
No	No	No	No	Yes	2 s		164
No	No	No	No	No	2+		229
No	No	No	No	No	3+, s n	TR	
No	No	No	No	No	2+,s		253
No	No	No	No	No	3+		
No	No	No	No	Yes			
No	Yes	No	No	No	3+,s,n	normal	262
Yes	Yes	No	No	No			247
No	No	No	No	No	2+		
No	No	No	No	Yes	2+,s,n	normal	155
No	No	No	No	No	2+,s		159
No	No	No	No	Yes	2+		
No	No	No	No	No	2+		185
No	No	No	No	Missing	2+		223
No	No	No	Yes	No	2 s		251
No	No	No	No	No	2+ , n		
No	No	No	Yes	Yes	4+,s,n	normal	702
No	No	No	No	Yes	3+,s,n		284
No	No	No	No	No	4+,s		1
No	No	Yes	No	No	3+,s,n		209
No	No	No	No	No	2+ s		
No	No	No	No	No	3+,s,n		238
No	No	No	No	No	4+,s		
No	Yes	No	Yes	No	2+,s		253
No	No	No	No	No	3+,	normal	250
No	No	No	No	No	1s	normal	4
No	No	No	No	No			
No	Yes	No	Yes	No	4 s		
No	No	No	No	No	4 s		2
No	No	No	No	No	2 , s n		
No	No	No	No	No	2		
No	No	No	No	No			
No	No	No	No	Yes	3 n		1
No	No	No	No	No	3 n		1
No	Yes	No	No	Yes	1 n		

anticentromereantibody	otherssystemicspecify	hrctchest
	osteoporosis	interstitial lung disease
		ILD
		early ILD
421		Liver heterogenicity
	osteoporosis	
		ILD
501		
		ILD
	hypothyroidism dm htn	ILD
		normal
		ILD, dialated esophagus
		NSIP
		normal
		normal
		ground glass opacities dilated oesophagus
190		
1		
1		

dateinterleukin61st	resultinterleukin61st	dateinterlekin62nd	resultinterleukinresult2nd

rodnansskinscoredate	rodnansskinscoredate2	rodnansskinscore1	rodnansskinscore2
05-08-2014		23	
13-04-2015		24	
14-02-2015		48	
15-07-2015		15	
12-03-2015		16	
14-03-2015		8	
01-02-2014		29	
13-11-2014		25	
01-10-2014		4	
17-02-2015		16	
22-11-2014		25	
04-05-2015		10	
31-07-2104		20	
26-11-2014		31	
20-03-2014		10	
25-02-2014		4	
15-03-2014		17	
20-03-2014		28	
02-10-2014		7	
25-06-2014		42	
09-07-2015		0	
20-10-2015		26	
16-10-2014		8	
14-10-2014		15	
11-05-2015		2	
18-04-2015		18	
18-01-2015		6	
28-03-2014		16	
		9	
03-09-2015		8	
27-11-2014		12	
27-02-2015		10	
20-04-2015		15	
30-04-2015		10	
10-02-2015		26	

రోగి సమాచార పత్రం

శీర్షిక: స్క్లెరోడెర్మా రోగులలో చర్మపు మరియు గోరులలో మార్పులు, రక్తపు ఇంటర్ల్యూకిన్-6 స్థాయి మరియు రాడ్నన్ తీవ్రత పద్ధతికి అనుబంధం సంబంధం.

అధ్యయనం యొక్క ఉద్దేశం:-

స్క్లెరోడెర్మా అనే వ్యాధికి ఖచ్చితమైన కారణం తెలియదు. ఇది ప్రధానంగా చర్మాన్ని ప్రభావితం చేసి, బిగువుగా అయ్యేలాగా చేస్తుంది. ఇది ఊపిరితిత్తులు, గుండె, జీర్ణశయాంతర వ్యవస్థను, రక్తనాళాలను కూడా ప్రభావితం చేయచ్చు. నేను ఈ అధ్యయనంలో ఈ రోగం వల్ల చర్మంలో కలిసే మార్పులను పరిశోధించబోతున్నాను. మరియు సహజంగా తెల్లరక్త కణాలు ఇంటర్ల్యూకిన్-6 అనే పదార్థాన్ని గ్రహిస్తాయి. ఈ పదార్థానికి మరియు చర్మగాయాలకు సంబంధం ఉందని తెలియనున్నది. అలాగే నేను డెర్మటోస్కోప్ అనే యంత్రాన్ని ఉపయోగించి గోర్లచుట్టూ ఉన్న చర్మపు యొక్క కేశనాళికలను పరిశీలించడానికి ఆసక్తిచూపుతున్నాను. ఈ యంత్రం కేశనాళికలను పెద్ద చిత్రంలో చూపించి, వ్యాధి యొక్క దశ అంచనా వేయటంలో సహాయపడుతుంది.

రోగి పాల్గొనడం యొక్క అంచనా వ్యవధి:-

డెర్మటాలజీ ఓ.పి.డి-11 లేదా ర్యుమటాలజీ ఆసుపత్రిలో ఉన్న రోగులు; మొదటిసారి మాత్రమే. రోగి తిరిగి మూడు నెలలు తరువాత

రావాలని సలహా ఇస్తారు. వచ్చినప్పుడు రక్త పరీక్ష చేయబడును.

విధానము యొక్క వివరములు:-

ఈ అధ్యాయంలో రోగి యొక్క సంబంధిత వివరాలు, చర్మ గాయాల యొక్క సమగ్ర పరీక్ష వివరాలు ఉంటాయి. డెర్మటోస్కోపీ యంత్రం ఉపయోగించి గోరు చుట్టూ ఉన్న చర్మపు కేశనాళికలను పరిక్షిస్తారు. కొంతమంది రోగులలో (లైంగ్రమైన చర్మ గాయాలు ఉన్నవారు) నుండి రక్తం సేకరించి ఇంటర్‌ల్యూకిన్-6 స్థాయి చూస్తారు. చర్మగాయాల యొక్క ఫోటోలు తీసుకోవచ్చు.

రోగి హాని తేదా అసౌకర్యము:-

ఈ అధ్యాయంలో ఎటువంటి చికిత్స లేదు, కావున ఈ అధ్యాయంలో ప్లాస్టానుటవలన రోగికి ఎటువంటి హాని జరగదు. ఈ అధ్యాయంలో భాగంగా అవడానికి రోగి ఎటువంటి అదనపు ఖర్చు పెట్టనవసరం లేదు.

రోగికి ప్రయోజనాలు:

ఈ అధ్యాయంనుండి సేకరించిన సమాచారం స్క్లెరోడెర్మా యొక్క చర్మ సంబంధ అంశాలను అర్థం చేసుకోవటంలో సహాయపడవచ్చును. అలాగే ఇది చికిత్స ఎంపికలో మరియు వ్యాధి యొక్క పరిస్థితి అర్థం చేసుకోవడంలో దోహద పడుతుంది.

గోప్యత

ఈ అధ్యయనం యొక్క పరిశోధకులకు మాత్రమే రోగి యొక్క వివరాలు అందుబాటులో ఉంటాయి. రోగి యొక్క వివరములు ఏ రూపంలో అయినా

మూడవ వ్యక్తికి వెల్లడించబడదు లేదా ప్రచురించబడదు.

పాల్గొనటం:

ఈ అధ్యయనంలో రోగి స్వచ్ఛందంగా పాల్గొంటారు. మరియు ఏ సమయంలో అయినా ఏ కారణం లేకుండా అధ్యయనం నుండి ఉపసంహరించుకోవచ్చు. అధ్యయనం నుండి ఉపసంహరించినను లేదా పాల్గొనడానికి తిరస్కరించినను రోగికి ఎటువంటి నష్టం కలుగదు.

అధ్యయనంలో పాల్గొనే రోగుల సుమారు సంఖ్య: 100

వివరాలకు సంప్రదించండి:-

డా॥ ప్రియా సారా కుర్యన్
పి.జి. రెజిస్ట్రార్
డి.వి. యల్ యూనిట్-1
సి.యం.సి. వెల్లూరు.

ఫోన్: 04162282054.

ఈ-మెయిల్: derm@cmcvellore.ac.in

అనుమతి పత్రం

పరిశోధన అధ్యయనంలో పాల్గొనటానికి అనుమతి

శీర్షిక :- స్క్లిరోడెర్మా రోగులలో చర్మపు మరియు గోరులలో మార్పులు, రక్తపు ఇంటర్ల్యూకిన్ - 6 స్థాయి మరియు రాడ్నన్ పద్ధతితో సంబంధం.

సంఖ్య :

పేరు :

సంతకం :

జనదినం :

తేది _____ న

(1) పైన ఇచ్చిన అధ్యయన సమాచారాన్ని చదివి, అర్థం చేసుకున్నానని నిర్ధారిస్తున్నాను; మరియు ప్రశ్నించుటకు అవకాశం కలిగియుంది

(2) ఈ అధ్యయంలో స్వేచ్ఛందంగా పాల్గొంటున్నాను; మరియు ఏ చట్ట పరమైన, వైద్య పరమైన కష్టాలు లేకుండా, ఏ కారణం లేకుండా ఏ సమయంలో అయినా అధ్యయనం నుండి ఉపసంహరించుకోవచ్చని తెలియజేసారు.

(3) నేను అధ్యయనం చేస్తున్న వ్యక్తికి మరియు వ్యక్తి తరుపున పనిచేస్తున్న వారికి, నియంత్రణ అధికారులకు, ప్రస్తుత, భవిష్యత్తు అధ్యయనముల కోసం నా వైద్య వివరాలు చూడటానికి అనుమతి

ఇస్తున్నాను. నేను అధ్యాయనం నుండి ఉపసంహరించుకున్నా నా వివరాలను చూడగలరు. ప్రచురించబడుతున్న తేక మూడవ వ్యక్తికి తెలియజేయబడే ఈ అధ్యాయనంలో నా వ్యక్తిగత వివరాలు బహిర్గతం చేయరనే నమ్ముచున్నాను.

(4) ఈ అధ్యాయము నుండి ఉద్భవించిన ఫలితాలను శాస్త్రీయ అవసరాల కోసం ఉపయోగించుకోవడానికి అంగీకరిస్తున్నాను.

(5) నేను ఈ అధ్యయనంలో పాల్గొనడానికి అంగీకరిస్తున్నాను.

(6) నేకరించిన రక్తం నిల్వ చేసి, మరిన్ని అధ్యయనాల కోసం వాడుచ్చు

సంతకం / వేలముద్ర -

తేదీ -

పేరు -

ప్రతినిధి సంతకము :

తేది :

పేరు :

సాక్షి సంతకం :

తేది :

పేరు మరియు చిరునామా :

நுகவல் படலம்

சூநாய்ச்சியின் நுவைப்பு :-

லிகிலி நோடெர்மா நோயினால் தாக்கப்பட்டவரின் தோல் தன்மையும், மார்பும் நுகந்தின் பெர்மோ லிகோமி அறிந்து, மேலும் இன்டர்லூகின்-6 அளவினை நோட்டான் தோல் கணக்கிட்டு மேற்கோடு ஒப்பிடுவது பார்க்கும் சூநாய்ச்சி.

சூநாய்ச்சியின் கருதுகோள் :-

லிகிலி நோடெர்மா என்ற தோல் வியாதி, உலகில் காரணம் இதுவரை அறியப்படவில்லை. இது தோலை மிகவும் கடினமாக்கும் இது நுரையீரல், இதயம், இரல் மார்பு இரத்தநாளங்களை பாதிக்கும். நமது இரத்தத்தில் உள்ள வெள்ளை அணுக்கள் இன்டர்லூகின் 6 என்ற எனப்படை சார்ந்தும். இது இந்த வியாதிக்கு ஒரு காரணியாகும். இந்த சூநாய்ச்சி பெர்மோன்கோப் என்ற கருவியும் நுகந்தில் உள் இருக்கும் இரத்தநாளங்களை சூநாய் வேகம். இதன் மூலம் இந்த வியாதி எந்த நிலையில் இருக்கிறது என்பதை கண்டறியலாம்.

ஆராய்ச்சியின் காலம் :-

நீங்கள் தோல் புறநோயாளி பிரிவு / டெர்மடாலஜி புறநோயாளி பிரிவில் வரும்போது / அல்லது உள்நோயாளியாக சேரும்போது ஆராய்ச்சியில் சேர்க்கப்படுவீர்கள்.
இதன்பிறகு 3 மாதம் கழித்து வந்து, இரத்த பரிசோதனை செய்யவேண்டும்.

ஆராய்ச்சி செயல்முறை :-

உங்களை பற்றிய தகவல்கள் சேகரிக்கப்படும், மற்றும் விவரமாக சோதனை செய்யப்படும்.
டெர்மோஸ்கோப்பி செய்து நகத்தின் உட்புறம் இருக்கும் இரத்தகுழாய் கண்டறிவர்.
சிலரின் இன்டர்லூகின் அளவை கணக்கிட இரத்த பரிசோதனை மேற்கொள்ளப்படும்.
தோலின் புகைப்படம் தேவை ஏற்ப்பின் எடுக்கப்படும்.

ஆராய்ச்சியினால் ஏற்படும் ஆபத்து :-

இந்த பரிசோதனையால் வேறெதுவும் எந்த ஆபத்தோ, பாதிப்போ உங்களுக்கு நேரிடாது.

ஏற்படும் நன்மை :-

சிகிச்சை முறைகளை கண்டறிய உதவும்.

இந்த ஆராய்ச்சியால் சேகரிப்பது முற்றும் இரகசியமாக வைக்கப்படும். இதில் F.பெருமாள் மட்டுமே உங்களை பற்றிய தகவலை அறிவர். வேறு எவரும் அறியமாட்டார்கள்

இதில் நீங்கள் பங்குபெறுவது, மற்றும் உங்களை சார்ந்தது. நீங்கள் எந்த நேரத்தில் வேண்டுமானாலும் விலகிக்கொள்ளலாம். இதனால் உங்கள் சிகிச்சையில் எந்த வேறுபாடும் இருக்காது.

<u>மேலும் தகவலுக்கு :-</u>

பிரியா சாரா குரியன்
முதுகலை மாணவர்
தோல் பிரிவு
சி.எம்.சி - வேலூர்
04162282054

ஒப்புதல் படிவம்

ஆராய்ச்சி தலைப்பு :- ஸ்கிளிரோடெர்மா நோயில் ஏற்படும் தோலின் மாற்றங்கள், மற்றும் நகத்தின் டெர்மோஸ்கோப்பி விவரம், மற்றும் இன்டர்லூக்கின் - 6 இரத்தத்தில் அளவினை நோயின் நிலையுடன் ஒப்பிடும் ஆராய்ச்சி.

பெயர் :-

பிறந்த தேதி / வயது :-

1) இந்த தகவல் படிவத்தை முழுவதுமாக படித்து புரிந்து கொண்டேன், கேள்வி மற்றும் சந்தேகங்கள் கேட்க வாய்ப்பு கிடைத்தது [ ]

2) இந்த ஆராய்ச்சியின் பங்கேற்பது என்னுடைய சுய முடிவு, மற்றும் எந்த நேரத்திலும் விலகிக் கொள்ளலாம் என்பதை அறிவேன் [ ]

3) என்னை பற்றிய தகவல்களை இந்த ஆராய்ச்சியை சேர்ந்தவர் எந்த நேரத்திலும் பார்க்கலாம், உபயோகபடுத்தலாம். [ ]

4) என்னை பற்றிய தகவல்களை பத்திரிகையில் அச்சிட சம்மதிக்கிறேன்.

5) இந்த ஆராய்ச்சியில் பங்கேற்கிறேன் [ ]

கையெழுத்து :- ஆராய்ச்சியாளர் -

தேதி :-

பெயர் :-

நுகவல் படலம்

சூநாய்ச்சியின் நுவைப்பு :-

லிகிலி நோடெர்மா நோயினால் தாக்கப்பட்டவரின் தோல் தன்மையும், மார்பும் நுகந்தின் பெர்மோ லிகோமி அறிந்து, மேலும் இன்டர்லூகின்-6 அளவினை நோட்டான் தோல் கணக்கிட்டு மேற்கோடு ஒப்பிடுவது பார்க்கும் சூநாய்ச்சி.

சூநாய்ச்சியின் கருதுகோள் :-

லிகிலி நோடெர்மா என்ற தோல் வியாதி, உலகில் காரணம் இதுவரை அறியப்படவில்லை. இது தோலை மிகவும் கடினமாக்கும் இது நுரையீரல், இதயம், இரல் மார்பு இரத்தநாளங்களை பாதிக்கும். நமது இரத்தத்தில் உள்ள வெள்ளை அணுக்கள் இன்டர்லூகின் 6 என்ற எனப்படை சார்ந்தும். இது இந்த வியாதிக்கு ஒரு காரணியாகும். இந்த சூநாய்ச்சி பெர்மோன்கோப் என்ற கருவியும் நுகந்தில் உள் இருக்கும் இரத்தநாளங்களை சூநாய் வேகம். இதன் மூலம் இந்த வியாதி எந்த நிலையில் இருக்கிறது என்பதை கண்டறியலாம்.

ஆராய்ச்சியின் காலம் :-

நீங்கள் தோல் புறநோயாளி பிரிவு / ருமட்டாலஜி புறநோயாளி பிரிவில் வரும்போது / அல்லது உள்நோயாளியாக சேரும்போது ஆராய்ச்சியில் சேர்க்கப்படுவீர்கள். இதன்பிறகு 3 மாதம் கழித்து வந்து, இரத்த பரிசோதனை செய்யவேண்டும்.

ஆராய்ச்சி செயல்முறை :-

உங்களை பற்றிய தகவல்கள் சேகரிக்கப்படும், மற்றும் விரிவாக சோதனை செய்யப்படும். டெர்மோஸ்கோபி செய்து நகத்தின் உட்புறம் இருக்கும் இரத்தக்குழாய் கண்டறிவர். சீரமின் இன்டர்லூகின் அளவை கணக்கிட இரத்த பரிசோதனை மேற்கொள்ளப்படும். தோலின் புகைப்படம் தேவைப்படின் எடுக்கப்படும்.

ஆராய்ச்சியினால் ஏற்படும் ஆபத்து :-

இந்த பரிசோதனையில் சேருவதால் எந்த ஆபத்தோ, பாதிப்போ உங்களுக்கு நேரிடாது.

ஏற்படும் நன்மை :-

சிகிச்சை முறைகளை கண்டறிய உதவும்.

இந்த ஆராய்ச்சியில் சேருவது முற்றும் இரகசியமாக வைக்கப்படும். இதில் ஈடுபடுபவர் மட்டுமே உங்களை பற்றிய தகவலை அறிவர். வேறு எவரும் அறியமாட்டார்கள்

இதில் நீங்கள் பங்குபெறுவது, மற்றும் உங்களை சார்ந்தது. நீங்கள் எந்த நேரத்தில் வேண்டுமானாலும் வெளியேறலாம் இதனால் உங்கள் சிகிச்சையில் எந்த வேறுபாடும் இருக்காது.

மேலும் தகவலுக்கு :-

பிரியா சாரா குரியன்

முதுகலை மாணவர்

தோல் பிரிவு

சி.எம்.சி - வேலூர்

04162282054

ஒப்புதல் படிவம்

ஆராய்ச்சி தலைப்பு :- ஸ்கிலிரோடெர்மா நோயில் ஏற்படும் தோலின் மாற்றங்கள், மற்றும் நகத்தின் டெர்மோஸ்கோப்பி விபரம், மற்றும் இன்டர்லூகின் - 6 திரவத்தின் அளவினை நார்மல் நிலையுடன் ஒப்பிடும் ஆராய்ச்சி.

பெயர் :-

பிறந்த தேதி / வயது :-

1) இந்த தகவல் படிவத்தை முழுவதுமாக படித்து புரிந்து கொண்டேன், கேள்வி மற்றும் சந்தேகங்கள் கேட்க வாய்ப்பு கிடைத்தது [ ]

2) இந்த ஆராய்ச்சியின் பங்குபெறுவது என்னுடைய சுய முடிவு, மற்றும் எந்த நேரத்திலும் விலகிக் கொள்ளலாம் என்பதை அறிவேன் [ ]

3) என்னை பற்றிய தகவல்களை இந்த ஆராய்ச்சியை சேர்ந்தவர் எந்த நேரத்திலும் பார்க்கலாம், உபயோகப்படுத்தலாம். [ ]

4) என்னை பற்றிய தகவல்களை பத்திரிகையில் அச்சிட சம்மதிக்கிறேன்.

5) இந்த ஆராய்ச்சியில் பங்குபெறுகிறேன் [ ]

கையெழுத்து :- ஆராய்ச்சியாளர் -

தேதி :-

பெயர் :-

OFFICE OF RESEARCH
INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE, VELLORE, INDIA.

Dr. B.J. Prashantham, M.A., M.A., Dr. Min (Clinical)
Director, Christian Counseling Center,
Chairperson, Ethics Committee.

Dr. Alfred Job Daniel, D Ortho, MS Ortho, DNB Ortho
Chairperson, Research Committee & Principal

Dr. Nihal Thomas,
MD., MNAMS., DNB (Endo), FRACP (Endo), FRCP (Edin), FRCP (Glasg)
Deputy Chairperson
Secretary, Ethics Committee, IRB
Additional Vice Principal (Research)

February 1, 2014

Dr. Priya Sara Kuryan
PG Registrar
Department of Dermatology, Venereology & Leprosy Unit
Christian Medical College
Vellore 632 004

Sub: **Fluid Research grant project:**
Cutaneous Profile and correlation of interleukin 6 levels in systemic sclerosis and nail fold dermatoscopy.
Dr. Priya Sara Kuryan, PG Registrar, Dr. Dincy Peter, Dr. Susanne Abraham, Dr. Leni George, Dermatology, Venereology & Leprosy Unit, Dr. Ruchika Goel, Dr. Debashish Danda, Dr. John Mathew, Clinical Immunology and Rheumatology.

Ref: IRB Min No: 8594 [OBSERVE] dated 04.12.2013

CHRISTIAN MEDICAL COLLEGE VELLORE INDIA

Dear Dr. Priya Sara Kuryan,

I enclose the following documents:-

1. Institutional Review Board approval 2. Agreement

Could you please sign the agreement and send it to Dr. Nihal Thomas, Addl. Vice Principal (Research), so that the grant money can be released.

With best wishes,

Dr. NIHAL THOMAS
MD., MNAMS., DNB(Endo), FRACP(Endo), FRCP(Edin), FRCP(Glasg)
SECRETARY - (ETHICS COMMITTEE)
Institutional Review Board,
Christian Medical College, Vellore - 632 002.

Dr. Nihal Thomas
Secretary (Ethics Committee)
Institutional Review Board

Cc: Dr. Dincy Peter, Dermatology, Venereology & Leprosy Unit, CMC

Ethics Committee Blue, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002.
Tel : 0416 - 2284294, 2284202 Fax : 0416 - 2262788, 2284481 E-mail : research@cmcvellore.ac.in

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Ref: IRB Min No: 8594 [OBSERVE] dated 04.12.2013

Dear Dr. Priya Sara Kuryan,

The Institutional Review Board (Blue, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project entitled "Cutaneous Profile and correlation of interleukin 6 levels in systemic sclerosis and nail fold dermatoscopy." on December 4th, 2013.

The Committees reviewed the following documents:

1. IRB application format
2. Curriculum Vitae' Dr. Priya Sara Kuryan, Dincy Peter, Susanne Abraham, Ruchika Goel, Debashish Danda, John Mathew, Leni George.
3. Consent form (English, Tamil, Telugu, Bengali & Hindi)
4. Information sheet (English, Tamil, Telugu, Bengali & Hindi)
5. Proforma
6. No of documents 1-5

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Deputy Chairperson
Secretary, Ethics Committee, IRB
Additional Vice Principal (Research)

The following Institutional Review Board (Blue, Research & Ethics Committee) members were present at the meeting held on December 4th, 2013in the CREST/SACN Conference Room, Christian Medical College, Bagayam, Vellore 632002.

Name	Qualification	Designation	Other Affiliations
Dr. T. Balamugesh	MBBS, MD(Int Med), DM, FCCP (USA)	Professor, Pulmonary Medicine, CMCH.	Internal, Clinician
Dr. Chandra Singh	MS, MCH, DMB	Professor, Urology, CMCH.	Internal, Clinician
Dr. Visalakshi	MPH, PhD	Lecturer, Dept. of Biostatistics, CMC.	Internal, Statistician
Dr. Anup Ramachandran	Ph. D	The Wellcome Trust Research Laboratory Gastrointestinal Sciences, CMCH.	Internal, Basic Medical Scientist
Dr. Rajesh Kannangai	MD, Ph D.	Professor & In-charge Retrovirus Laboratory (NRL under NACO), Department of Clinical Virology, CMCH.	Internal, Clinician
Dr. Srinivasa Babu	M.Sc, Ph.D.	Senior Scientist, Neurological Sciences, CMCH.	Internal, Basic Medical Scientist
Dr. Anand Zachariah	MBBS, PhD	Professor, Medicine, CMCH.	Internal, Clinician
Dr. Vivek Mathew	MD (Gen. Med.) D.M (Neuro) Dip. NB (Neuro)	Professor, Neurology, CMC	Internal, Clinician
Dr. Bobby John	MBBS, MD, DM, Ph D, MAMS	Professor, Cardiology, CMCH.	Internal, Clinician
Mrs. Pattabiraman	B. Sc, DSSA	Social Worker, Vellore	External, Lay person
Mr. C. Sampath	B. Sc, BL	Legal Expert, Vellore	External, Legal Expert

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Deputy Chairperson
Secretary, Ethics Committee, IRB
Additional Vice Principal (Research)

Dr. Vathsala Sadan	M.Sc, PhD	Professor, Community Health Nursing, CMCH.	Internal, Nurse
Dr. B. J. Prashantham	MA(Counseling Psychology), MA(Theology), Dr. Min(Clinical Counselling)	Chairperson, Ethics Committee, IRB. Director, Christian Counseling Centre, Vellore	External, Social Scientist
Dr. Anuradha Rose	MBBS, MD	Assistant Professor, Community Health, CMCH.	Internal, Clinician
Dr. Jayaprakash Muliyil	B. Sc, MBBS, MD, MPH, Dr PH (Epid), DMHC	Retired Professor, Vellore	External, Scientist & Epidemiologist
Mr. Samuel Abraham	MA, PGDBA, PGDPM, M. Phil, BL	Sr. Legal Officer, CMCH.	Internal, Legal Expert
Dr. Denise H. Fleming	B. Sc (Hons), PhD	Honorary Professor, Clinical Pharmacology, CMCH.	Internal, Scientist & Pharmacologist
Dr. Nihal Thomas	MD, MNAMS, DNB(Endo), FRACP(Endo) FRCP(Edin) FRCP (Glasg)	Professor & Head, Endocrinology. Additional Vice Principal (Research), CMCH. Deputy Chairperson, IRB, Member Secretary (Ethics Committee), IRB	Internal, Clinician

We approve the project to be conducted as presented.

The Institutional Ethics Committee expects to be informed about the progress of the project, any **adverse events** occurring in the course of the project, any **amendments in the protocol and the patient information / informed consent**.

IRB Min No: 8595 [OBSERVE] dated 04.12.2013

Ethics Committee Blue, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002.
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MD., MNAMS., DNB (Endo), FRACP (Endo), FRCP (Edin), FRCP (Glasg)
Deputy Chairperson
Secretary, Ethics Committee, IRB
Additional Vice Principal (Research)

On completion of the study you are expected to submit a copy of the **final report**. Respective forms can be downloaded from the following link: http://172.16.11.136/Research/IRB_Polices.html in the CMC Intranet and in the CMC website link address: http://www.cmch-vellore.edu/static/research/Index.html.

Fluid Grant Allocation:

A sum of 99,725 INR (Rupees Ninety Nine Thousand Seven Hundred and Twenty Five) will be granted for 2 years.

Yours sincerely

NOT TO BE MINISTERED UNTO BUT TO MINISTER
CHRISTIAN MEDICAL COLLEGE
VELLORE
INDIA

Dr. Nihal Thomas
Secretary (Ethics Committee)
Institutional Review Board

Dr. NIHAL THOMAS
MD.,MNAMS.,DNB(Endo),FRACP(Endo),FRCP(Edin),FRCP(Glasg)
SECRETARY - (ETHICS COMMITTEE)
Institutional Review Board,
Christian Medical College, Vellore - 632 002.

Cc: Dr. Dincy Peter, Dermatology, Venereology & Leprosy Unit, CMC

IRB Min No: 8594 [OBSERVE] dated 04.12.2013

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रोगी जानकारी पत्र

→ पढाई का शीर्षक

स्क्लीरोडरमा रोगी में त्वचा और नाखून की जाँच स्कोपी द्वारा और खून में इंटरल्यूकिन - 6 की मात्रा का उत्तरदायित्व आधुनिक रोडनन त्वचा स्कोर के साथ

→ Research जाँच का कारण

स्क्लीरोडरमा एक बिमारी है जिसका कारण नही पता है। यह मुख्यता त्वचा में खिचाव करता है और फेफड़े, दिल, आंतरडिया और खून की नालियों में बिमारी फैलाता है। इस पढाई में मैं त्वचा के अंदर स्क्लीरोडरमा के कारण आने वाले बदलाव को देखूंगी। रक्त खून cell से बनने वाला एक पदार्थ इंटरल्युकिन - 6 को भी देखूंगी। फिर मैं, दूरबीन से नाखूनो के खून की नालियों का जाँच करूंगी जिससे मुझे जानकारी मिलेगी की बिमारी कहा तक फैली है।

→ पढाई में सम्मलित होने का समय

त्वचा क्लिनिक - 2 OPD / रूमाटोलोजी क्लिनिक OPD और वार्ड के रोगी जिनको यह बिमारी है, वे इस पढाई में सम्मलित होने के लिए और उनको सूचित किया जाएगा की वह तीन महिनो के बाद खून के जाँच के लिए दुबारा आए।

→ जाच कैसे होगा

इस पढाई मे रोगी से कुछ प्रश्न पूछे जाएंगे और त्वचा की जाँच होगी। स्कोपी द्वारा नाखून के खून की नलियो से जाँच होगी। कुछ विशेष रोगियो मे खून की जाँच होगी। त्वचा रोग के चित्र भी लिए जाएंगे।

→ रोगियो के लिए असुविधा और खतरे के कारण

इस पढाई मे रोगियो को कोई खतरा और असुविधा नही होगी और रोगियो को अतिरिक्त पैसे देने की जरूरत नही है।

→ रोगियो को लाभ

यह पढाई इस बिमारी मे नए और अधिक इलाज करने मे मदद करेगी।

→ दूसरो के लिए लाभ

इस पढाई से मिलने वाले जानकारी से त्वचा रोग के बारे मे और अधिक पता चलेगा। इंटरल्युकिन-6 और स्कोपी द्वारा नाखून की जाँच से आने वाले दिनो मे इस बिमारी के बहतर इलाज मे मदद करेगा।

→ रहस्य

सिर्फ इस पढाई से जुडे हुए चिकित्सक आपके ईकोई देख पाएंगे और आपकी बिमारी और आपके बारे मे सब जानकारी गुप्त रखी जाएगी।

→ शामलित होने के लिए

रोगी अपनी इच्छा से इस पढाई मे शामलित होंगे।
वह किसी भी समय और कारण से इस पढाई को छोड़
सकते है। इस से उन्हे को दुण्ड या को लाभ नही मिलेगा।

इस पढाई मे लगभग 100 रोगियो के भाग लेने की
जरूरत है।

विषयों के लिए सूचित सहमति फॉम का प्रारूप

एक शोध अध्ययन म भाग लेने के लिए सूचित सहमति फॉम

अध्ययन शीषक: Cutaneous प्रोफ़ाइल और नाखून संशोधित Rodnan त्वचा गंभीरता स्कोर के साथ 6 स्तरों सहसंबंध इंटरल्यूकिन scleroderma रोगियों और सीरम का त्वचा का लंस गुना.

अध्ययन संख्या: _____

विषय के प्रथमाक्षर : _____ रोगी का नाम: _____

जन्म / आयु का तिथि : _____

(विषय)

(म) म मने पढ़ा और समझा उपरोक्त अध्ययन के लिए _____ दिनांकित जानकारी शीट और सवाल पूछने का अवसर मिला है का है कि इस बात का पुष्टि .

(ii) म अध्ययन म मेरी भागीदारी स्वैच्छिक है और म अपने चिकित्सा देखभाल या प्रभावित किया जा रहा कानूनी अधिकार के बिना , किसी भी कारण बताए, किसी भी समय म वापस लेने के लिए स्वतंत्र हूँ कि समझते ह.

(iii) म चिकित्सीय परीक्षण के प्रायोजक , प्रायोजक का ओर से काम कर रहे अन्य लोगों , आचार समिति और नियामक अधिकारियों वतमान अध्ययन के संबंध म और किसी भी आगे अनुसंधान म दोनों मेरे स्वास्थ्य रिकॉड को देखने के लिए मेरी अनुमति का जरूरत नहीं होगी समझते ह कि म परीक्षण से वापस लेने , भले ही यह करने के संबंध म आयोजित किया जा सकता है . म इस का उपयोग करने के लिए सहमत ह . हालांकि, म अपनी पहचान तीसरे पक्ष को जारी या प्रकाशित किसी भी जानकारी म नहीं बताया जाएगा कि समझते ह.

(चतुथ) म इस तरह का इस्तेमाल केवल वैज्ञानिक उद्देश्य (ओं) के लिए है, बशत कि इस अध्ययन से उठता है कि किसी भी डेटा या परिणाम के इस्तेमाल को प्रतिबंधित करने के लिए सहमत नहीं है.

(v) म उपरोक्त अध्ययन म भाग लेने के लिए सहमत ह.

(vi) म संग्रहित रक्त का नमूना किसी भी भविष्य के अनुसंधान म इस्तेमाल किया जा सकता है कि इस बात से सहमत .

विषय / कानूनी तौर पर स्वीकाय के हस्ताक्षर (या अंगूठे का निशान)

दिनांक: _____ / _____ / _____

हस्ताक्षरकता का नाम: _____ हस्ताक्षर:

या

प्रतिनिधि: _____

दिनांक: _____ / _____ / _____

हस्ताक्षरकता का नाम: _____

अन्वेषक के हस्ताक्षर: _____

दिनांक: _____ / _____ / _____

अध्ययन जांचकता का नाम: _____

गवाह का हस्ताक्षर : _____

दिनांक: _____ / _____ / _____

नाम और गवाह का पता: _____

অধীন ব্যক্তির সম্মতিপত্র

গবেষনায় অংশগ্রহণ করার তথ্যপূর্ণ সম্মতিপত্র—

গবেষনার নাম: বিউটেনিয়াস প্রফাইল অ্যান্ড ফেনল ভেরমাটোগ্রেফি অ্যান্ড সিরাম ইন্ডারলিউকিন-৬ লেভেলস্ কোরিলেশান উইদ মডিফাইড রোডনান স্কিন সিভারিটি স্কোর।

পরীক্ষা নং—

অংশগ্রহনকারীর নাম—

অংশগ্রহনকারীর স্বাক্ষর—

জন্মতারিখ/বয়স—

(অংশগ্রহনকারী)

১. আমি দৃঢ়ভাবে প্রতিজ্ঞা করছি যে আমি উপরোক্ত তথ্যপত্র, তারিখ _____ ভালোভাবে পড়েছি, বুঝেছি এবং মনোনিবেশ প্রশ্ন করার সুযোগ পেয়েছি।

i) আমি বুঝেছি যে উপরোক্ত পরীক্ষায় আমার আংশগ্রহণ সম্পূর্ণ স্বেচ্ছায় এবং যে কোনো সময় বিনা কারণ দর্শিয়ে আমি বিচ্যুত হতে পারি, এবং তাতে আমার চিকিৎসা কোনোভাবেই ক্ষতিগ্রস্থ হবে না,

ii) আমি বুঝেছি যে এই গবেষনার স্থানসমূহ, স্থানসমূহের অধীনে কর্মরত ব্যক্তিরা, প্রতিষ্ঠান কমিটি এবং হাসপাতাল কর্তৃপক্ষ ~~আমি~~ বিনা অনুমতিতে আমার সমস্ত চিকিৎসা সংক্রান্ত তথ্যাবলি ব্যবহার করতে পারবেন এই গবেষনা এবং এই সংক্রান্ত পরবর্তী কোনো গবেষনার ক্ষেত্রে, আমি সাক্ষাৎকারে বিচ্যুত হলেও, ~~আমি~~ আমি এও বুঝেছি যে কোনো ক্ষেত্রেই আমার পরিচয় কোনো ভাবেই প্রকাশ পাবে না,

iii) এই গবেষনা থেকে পাওয়া কোনো তথ্য আমি সম্পূর্ন স্বাধীনভাবে ব্যবসার ব্যবহার অনুমতি দিচ্ছি, কিন্তু শুধুমাত্র বিজ্ঞানের স্বার্থে,

৬) আমি উপরোক্ত পরীক্ষায় অংশগ্রহণ করার সম্মতি জানাচ্ছি।

অংশগ্রহণকারীর স্বাক্ষর বা আঙুলের ছাপ,

তারিখ: ——/——/——

দস্তখতকারীর নাম: _____

দস্তখত _____

প্রতিনিধি :_____

তারিখ: __/__/__

স্বাক্ষরকারীর নাম: _____

পরীক্ষাকারীর স্বাক্ষর: _____

তারিখ: __/__/__

পরীক্ষাকারীর নাম: _____

১ম সাক্ষীর নাম: _____

তারিখ: __/__/__

১ম সাক্ষীর নাম এবং ঠিকানা:-

রোগীর তথ্য পত্রক
স্টাডি শিরোনাম:
Cutaneous প্রোফাইল এবং scleroderma রোগীদের ভাঁজ dermatoscopy এবং সিরাম Interleukin থাকা 6 মাত্রা বার পরিমার্জিত Rodnan চামড়া তীব্রতা স্কোর সঙ্গে সংগতি
গবেষণার উদ্দেশ্য :
Scleroderma যা সঠিক aetiology পরিচিত না হয় , যার জন্য একটি রোগ . Scleroderma প্রধানত জোরদার যার ফলে ত্বক প্রভাবিত করে. এটি ফুসফুস, হার্ট, gastro অন্ত্রের সিস্টেম এবং রক্ত জাহাজ প্রভাবিত করতে পারে. এই গবেষণায় আমি রোগের সঙ্গে যুক্ত বিভিন্ন চামড়া প্রকাশ অধ্যয়ন মনস্থ করা. এছাড়াও করা Interleukin 6 (আইএল -6) নামে পরিচিত আমাদের শরীরের রক্তের শ্বেতকণিকা দ্বারা নিঃসৃত একটি বিশেষ পদাথ scleroderma চামড়ার ক্ষত সঙ্গে যুক্ত করা হয়. আমি আরও একটি dermatoscope ব্যবহার করে নখ প্রায় চামড়ায় capillaries দেখতে মনস্থ করা. এই capillaries একটি বিবধিত চিত্র দেয় এবং রোগের পযায়ে ভবিষ্যদ্বাণী করতে সাহায্য করে.
বিষয়ের অংশগ্রহণ প্রত্যাশিত সময়কাল :
শুধু Dermatology ইউনিট এ রোগীর উপস্থাপনার সময় - scleroderma সঙ্গে দ্বিতীয় OPD / বাতরোগসংক্রান্ত OPD / ইন রোগীদের . রোগীর রক্ত পরীক্ষা করা হবে , যা সময় 3 মাস পরে অনুসরণ আপ আসতে adviced করা হবে না.
পদ্ধতি বণনা :
এই গবেষণায় রোগীর প্রাসঙ্গিক বিবরণ এবং ত্বকের ক্ষত বিস্তারিত পরীক্ষা রেকর্ডিং জড়িত হবে. একটি dermatoscopy আঙুল নখ প্রায় capillaries দেখতে সঞ্চালন করা হবে . নিবাচিত রোগীদের (ব্যাপক চামড়া জড়িত রোগীদের) একটি রক্তের নমুনা সংগ্রহ Interleukin 6 পরিমাপের জন্য সংগ্রহ করা হবে. ত্বকের ক্ষত ক্লিনিকাল ফোটোগ্রাফ নেওয়া হতে পারে .
ঝুঁকি বা বিষয় discomforts :
গবেষণায় কোনো ট্রায়াল চিকিত্সা অন্তর্ভুক্ত নয় , গবেষণায় অংশগ্রহণ কারণে রোগীর জন্য কোন অতিরিক্ত ঝুঁকি নেই. রোগীর গবেষণায় অংশ গ্রহণ করে কোন অতিরিক্ত খরচ বহন করবে না.
বিষয় সুবিধাসমূহ:
এটি অবস্থার আরও ব্যবস্থাপনায় সাহায্য করতে পারে.
অন্যদের সুবিধাসমূহ:
এই গবেষণায় থেকে সংগ্রহ করা তথ্য scleroderma এর cutaneous দিক বুঝতে সাহায্য করতে পারে . একটি আইএল 6 ভূমিকা বোঝার এবং ভাঁজ dermatoscopy থাকা সম্ভাব্য চিকিত্সা অপশন অন্বেষণ সেইসাথে scleroderma এর পূবাভাসের অবদান ভবিষ্যতে সাহায্য করতে পারে.
গোপনীয়তা :
শুধু এই গবেষণা তদন্তকারীরা রোগীর চিকিৎসা রেকর্ড অ্যাক্সেস করতে সক্ষম হতে হবে. রোগীর পরিচয় কোনো আকারে প্রকাশ করা বা তৃতীয় পক্ষের মুক্তি বা প্রকাশ করা হবে না .

অংশগ্রহণ :
সম্পূণ স্বেচ্ছাসেবী গবেষণা এবং রোগীর রোগীর অংশগ্রহণ কোন নির্দিষ্ট কারণ ছাড়াই জানায় , যে কোনো সময় গবেষণা থেকে নিজেকে প্রত্যাহার করার বিনামূল্যে. অংশগ্রহণের বা গবেষণা থেকে সরে আসায় অস্বীকার যা রোগীর অন্যথায় এনটাইটেল করা হয় বেনিফিট কোন শাস্তি বা হানি হবে না.
বিষয় আনুমানিক সংখ্যা গবেষণা মধ্যে নাম নথিভুক্ত - 100
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