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Nailbed Videocapillaroscopy – Key To Early Diagnosis And Prognosis In Systemic Sclerosis

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Abstract
Background: *Systemic sclerosis (SSc) is a systemic autoimmune disease characterised by widespread cutaneous and visceral fibrosis, small-vessel vasculopathy, and presence of autoantibodies against several cellular antigens. It is a heterogeneous disease with respect to the extent of skin involvement and internal organ severity, ranging from limited cutaneous SSc, with less serious involvement of the internal organs, to diffuse cutaneous SSc, characterised by extensive skin involvement and often rapidly progressive visceral involvement which can lead to complications like Pulmonary arterial hypertension (PAH) and Interstitial Lung Disease (ILD). Our main objective is to associate capillary abnormalities in patients of systemic sclerosis mainly with PAH and ILD for early detection and intervention to increase their longevity.*
Material and Methods: *This is a hospital based cross sectional study done in 1 year in Assam Medical College and Hospital , India from February 2020 to January 2021. All cases of Systemic Sclerosis aged 12 years and above attending outpatient departments or in various wards of Assam Medical College and Hospital, who fulfilled the ACR criteria for diagnosis of SSc have been taken up for the study. Nailbed capillaroscopy, echocardiography, Pulmonary Function Test, HRCT thorax, antibody profile and routine blood investigations were done.*
Observations: *A total of 61 patients were studied. The mean age was 39.18 ±13.48 years and the median age 38 years. In our study, 13 patients were male (21.31%) and 48 were female (78.69%). Female to Male ratio was 3.69:1. Maximum patients (93.44%) presented with Raynaud's Phenomenon which was followed by sclerodactyly in 81.96 % patients, 14 patients (22.95%) presented with PAH and 43(70.49%) with ILD. No patient presented with renal insufficiency. Out of these 14 patients with PAH, 10 showed late SSC pattern (71.43%), 4 patients (28.57%) showed active SSc pattern and 0 patient had early SSc pattern. Patients with ILD showed predominantly Active nailbed changes (51.16%). PAH and ILD have been found to have statistically significant association (p <0.05) with nailbed capilllaroscopy changes in our study.*
Conclusions: *Nailbed Video Capillaroscopy is hence a magical tool for – 1)Early diagnosis of systemic sclerosis, 2) Early prediction of complications 3) a tool that can prompt us to take effective measures to reduce mortality and morbidity in these patients. It is a cheap, non-invasive and handy tool. While limited research is available in this aspect, various studies are being done lately to see the immense potential of this tool in the field of Systemic Sclerosis.*
Key Words*: systemic sclerosis, nailbed video capillaroscopy, prognosis, pulmonary arterial hypertension, interstitial lung disease*

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I. Introduction

Systemic sclerosis (SSc) is a systemic autoimmune disease characterised by widespread cutaneous and visceral fibrosis, small-vessel vasculopathy, and presence of autoantibodies against several cellular antigens. It is a heterogeneous disease with respect to the extent of skin involvement and internal organ severity, ranging from limited cutaneous SSc, with less serious involvement of the internal organs, to diffuse cutaneous SSc, characterised by extensive skin involvement and often rapidly progressive visceral involvement . Although survival in SSc has improved in recent decades, SSc is still associated with significant morbidity and mortality rates. Previous studies have reported increased mortality in patients with older age, male sex, diffuse cutaneous SSc, and severe involvement of lungs, heart and kidneys.

Patients of SSc have been broadly grouped into diffuse cutaneous and limited cutaneous subsets defined by the pattern of skin involvement, as well as clinical and laboratory features. Extensive skin induration ascending from distal to proximal limbs and the trunk is seen in cases of Diffuse SSc(dcSSc). They are more prone to early interstitial lung disease and acute renal involvement.

In contrast, patients with limited cutaneous SSc (lcSSc) present with Raynaud's years before other manifestations set in. In these patients, skin involvement remains limited to the fingers (sclerodactyly), distal limbs (elbows), and face, and the trunk is not affected.

Calcinosis cutis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia, seen in some lcSSc patients, together is termed the CREST syndrome. Visceral organ involvement in lcSSc has insidious progression. Complications like pulmonary arterial hypertension (PAH), interstitial lung disease, hypothyroidism, and primary biliary cirrhosis may occur late. Presence of Raynaud's phenomenon and other characteristic features of SSc in the absence of skin thickening has been termed as SSc sine scleroderma.[1,2]

Pulmonary arterial hypertension, interstitial lung disease , scleroderma renal crisis and cardiac involvement remain some of the dreaded complications of the disease. Nailfold Video capillaroscopy (NVC) is a useful tool to diagnose Ssc and predict these complications.

EPIDEMIOLOGY

SSc is an acquired sporadic disease. It has a worldwide prevalence and affects all races. In the United States, the incidence is estimated at 9–19 cases per million per year.[1] The only community-based survey of SSc yielded a prevalence of 286 cases per million with an estimated 100,000 cases in the United State. Australia, England and Japan have a lower prevalence. Age, gender, and ethnicity play an important role in disease susceptibility.

In case of gender, SSc shows a strong female preponderance (4.6:1), which is most pronounced in the childbearing years and declines after menopause.[1] Although SSc can present at any age, the peak age of onset for both limited and diffuse cutaneous forms is around 30–50 years.The incidence is higher in blacks than whites, and disease onset occurs at an earlier age. Furthermore, blacks are more likely to have diffuse cutaneous disease associated with interstitial lung involvement and a worse prognosis.

No standardized studies on prevalence of the disease has been done in India. The reported prevalence based on a study in north India by Minz et al. is 120 cases per million. This study had showed that 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 and consisted of patients with connective tissue disorders and who had ANA positivity. The limitation of the study was that there was no well defined diagnostic criteria and the study was limited to north India.[3]

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. 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. The survival rate is dependent on the internal organ involvement and has significantly improved over the past years due to introduction of new drugs. The estimated 10 year survival rate is 70 to 80%.[4]

ETIOLOGY AND PATHOPHYSIOLOGY

The pathological process of Systemic Sclerosis involves three distinct features; micro vascular damage (vasculopathy) that leads to vessel obliteration, fibroblast dysfunction with excessive collagen production, and dysregulation of the immune system resulting in the production of disease-specific serum autoantibodies, most often ATA and ACA antibodies. IL-6 has been found to play an important role in immune mediated damage. Both environmental and genetic factors are potential risk factors for SSc. Scleroderma-like syndromes have been described after exposure to different factors; including exposures with contaminated rapeseed oil in 1981 in Spain, exposure with vinyl chloride in the mid 60`s and development of nephrogenic systemic fibrosis after administration of gadolinium contrast material for magnetic resonance imaging in the setting of renal insufficiency. Lately, gastrointestinal (gut) micro biota has been discussed as an interesting possible environmental factor for other diseases .[5,6]

The disease has been classified as Diffuse cutaneous Systemic sclerosis (dcSsc) and Limited cutaneous Systemic sclerosis (lcSsc).

Nailbed Capillaroscopy :

Microvascular abnormalities are one of the most important findings in collagen vascular diseases. Such changes cause clinical features (e.g., Raynaud‟s phenomenon or digital ulcer) or structural abnormalities which can be easily assessed with nailfold capillaroscopy (NFC). Brown and O'Leary were the first people to describe

the micro vascular abnormalities during Raynaud's phenomenon. Abnormal findings in the nail fold capillary network include[7,8] :

1. Architectural derangement
2. Capillary density changes
3. Megacapillary and enlarged loops
4. Microhemorrhages
5. Angiogenesis.

It is a cheap and handy tool to diagnose Systemic Sclerosis and has been incorporated into the ACR diagnostic Criteria. It can differentiate between primary and secondary Raynauds syndrome and is an indicator of microvascular damage. Hence this study has been taken up to study microvascular changes in nailbed and to associate these changes with systemic manifestations like pulmonary artery hypertension (PAH) and interstitial lung disease (ILD) and use this tool to predict prognosis of the disease.

Approximately 40-50 patients of SSC attend Rheumatology OPD of Assam Medical College and Hospital yearly .Most of these patients either come at a late stage or are misdiagnosed at the periphery in their initial years of disease onset. By the time these patients show up in the OPD of our hospital , they develop significant morbidity. Nail fold capillaroscopy is a tool that can be used to make an early diagnosis in patients of SSC when they present with Raynauds/ arthralgia/ digital ulcers etc. It can also be used to differentiate between primary and secondary Raynauds phenomenon .Therefore, an attempt has been made in this study to assess the association between nailbed capillaroscopic findings with morbidities or complications in patients of systemic sclerosis so that an early detection can help in appropriate and timely intervention in these patients and improve the survival rates. Hence this study was performed with the following aims and objectives :

- To study nail bed capillaroscopic findings in patients of Systemic Sclerosis
- To find out the presence of Pulmonary Arterial Hypertension and Interstitial Lung Disease in patients of Systemic Sclerosis
- To assess the association of Nailbed capillaroscopic findings with Pulmonary Arterial Hypertension and Interstitial Lung Disease in Systemic Sclerosis

II. Materials And Methods

PLACE OF STUDY

Assam Medical College and Hospital

DURATION OF STUDY

One year (1st February 2020 to 31st January 2021)

DESIGN OF THE STUDY

Hospital based cross sectional study

STUDY POPULATION

All cases of Systemic sclerosis diagnosed by American College of Rheumatology preliminary criteria attending Rheumatology OPD and other outpatient departments or inpatient wards of department of Medicine at Assam Medical College and Hospital.[1] A total of 61 patients were studied.

INCLUSION CRITERIA:

- All SSC patients attending Rheumatology OPD and other outpatient department or in various wards of Department of Medicine at Assam Medical College and Hospital, who fulfilled the American College of Rheumatology preliminary criteria for the diagnosis of SSC have been taken up for the study.
- Age group: 12 years or above

EXCLUSION CRITERIA:

- Age less than 12 years.
- Primary cardiovascular disease
- Obstructive lung disease
- Patients who do not give consent

INFORMED CONSENT:

All the patients were given an explanation of the study and informed written consent were taken from them or their attendants before enrolment into the study.

ETHICAL CLEARANCE:

Ethical clearance was taken from the Institutional Ethics Committee(H), Assam Medical College and Hospital, Dibrugarh.

METHODOLOGY :

Cases were clinically examined and grouped under Diffuse cutaneous SSC (dcSSC), Limited cutaneous SSC (lcSSC) and Overlap syndrome with SSC predominance. Complete blood counts, renal function tests, liver function tests, thyroid function tests , autoantibody profile, HRCT thorax , Pulmonary Function Tests were done. Echocardiography by SIEMENS L10-5 LINEAR ARRAY was done and evidence of pulmonary and/or

tricuspid regurgitation with tricuspid insufficiency peak gradient (TIPG) of more than or equal to 30mm Hg was used for detection of PAH. *Nail bed capillaroscopy* by BOSHIDA Nailbed Video Capillaroscope*(*Model : BD-WXH880) was done to look for microvascular abnormalities and Scleroderma pattern of capillary changes were grouped as early , active and late patterns.

STATISTICAL ANALYSIS:

Data collected are tabulated in Microsoft Excel Worksheet and computer based analysis is performed using Statistical Product and Service Solutions (SPSS) 20.0 software (SPSS , Chicago , Illinois , USA) and Microsoft Excel 2010. The categorical variables are summarised as proportions and percentages. Results on continuous measurements are presented as Mean ± Standard Deviation. Discrete data are expressed as number (%) and are analysed using Chi Square test or Fisher's exact test . For all analysis, the statistical significance is fixed at 5% level ($p < 0.05$).

III. Results

The study consisted of 61 cases of Systemic Sclerosis who attended Rheumatology OPD, other outpatient departments or admitted in various wards in the Department of Medicine, Assam Medical College, Dibrugarh during the period of February 2020 to January 2021. Out of 61 cases, the mean age was 39.18±13.48 years and the median age 38 years. 13 were male (21.31%) and 48 were female (78.69%). Female to Male ratio was 3.69:1. Maximum patients 57 (93.44%) presented with Raynaud's Phenomenon which was followed by sclerodactyly in 81.96 % patients. 14 patients (22.95%) presented with PAH and 43(70.49%) with ILD. No patient presented with renal insufficiency. Amongst all SSC cases, maximum (32) were Diffuse Systemic Sclerosis patients which accounted for 52.45%. 16.41 % patients had limited cutaneous SSc and 31.14% had Overlap syndrome with SSc predominance.

Pulmonary Hypertension was present in 14 out of 61 patients (22.95%). 50% these cases had Diffuse cutaneous SSC followed by Limited cutaneous SSC (35.71) . 14.29% patients with PAH had overlap syndrome with SSC preponderance.

TABLE 1: CAPILLAROSCOPIC FINDINGS IN ALL CASES

	LIMITED CUTANEOUS SSC		DIFFUSE CUTANEOUS SSC		OVERLAP SYNDROME WITH SSC PREPONDERANCE	
	No. of cases	%	No. of cases	%	No. of cases	%
EARLY	2	20	2	6.25	6	31.57
ACTIVE	5	50	16	50	9	47.36
LATE	3	30	14	43.75	4	21.07
TOTAL	10	100	32	100	19	100

Table 1 shows that all the cases (61) had scleroderma pattern on nailfold capillaroscopy. Maximum patients with LcSSc had Active capillaroscopic changes (50%) and DcSSc cases had a maximum of Active changes (50%) followed by Late capillaroscopic changes (43.75%). Overlap syndrome also showed similar patterns with Active changes (47.36%) being the highest but was followed by Early changes with 31.57%.

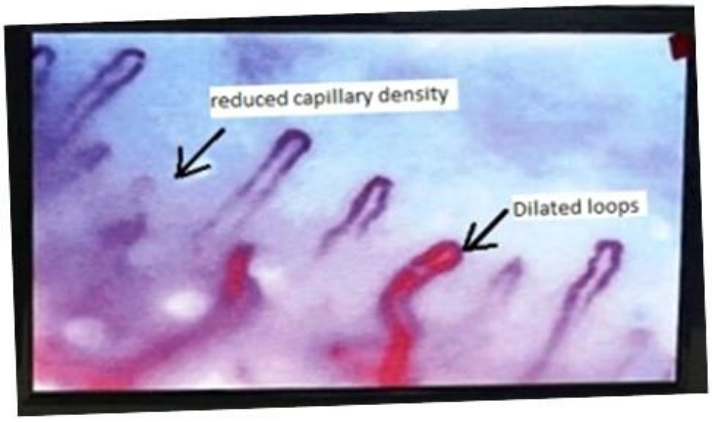

FIGURE 1 : Early scleroderma pattern

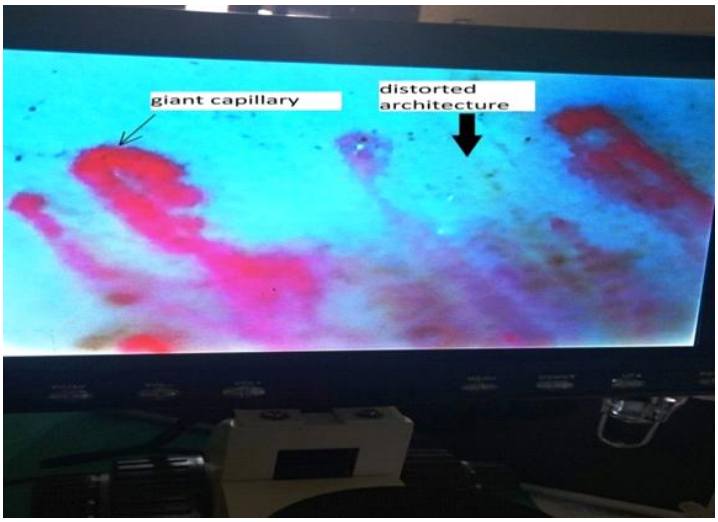

FIGURE 2 : Active scleroderma pattern

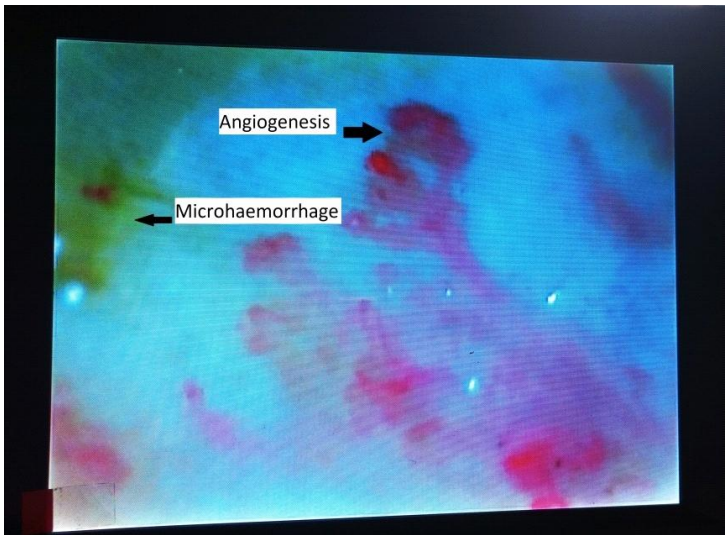

FIGURE 3 : : Late scleroderma pattern with severe architectural derangement

TABLE 2 : CAPILLAROSCOPIC FINDINGS IN PATIENTS WITH PAH

	Early	**Active**	**Late**
Number of cases (n)	**0**	**4**	**10**
Percentage (%)	**0**	**28.57**	**71.43**

TABLE 3 : RELATION OF NAILBED CAPILLAROSCOPIC FINDINGS WITH PAH IN SSC CASES

PAH ↓	NAILBED CAPILLAROSCOPIC FINDINGS			P VALUE
	EARLY	ACTIVE	LATE	
POSITIVE	0	4	10	0.00355
NEGATIVE	10	26	11	

Fisher's Exact Probability test shows that association of PAH with nailfold capillaroscopic changes is statistically significant(P <0.05).

TABLE 4 : RELATION OF NAILBED CAPILLAROSCOPIC FINDINGS WITH ILD

ILD	EARLY	ACTIVE	LATE	P VALUE
POSITIVE	2	22	19	0.0002
NEGATIVE	8	8	2	

Table 4 shows that relation between Nailbed Capillaroscopic findings and ILD is statistically significant ($P < 0.05$).

TABLE 5 : RELATION OF MODIFIED RODNAN SCORE WITH CAPILLAROSCOPIC PATTERNS

Modified Rodnan Score	**Early Nailbed Changes Cases (N)**	**Early Nailbed Changes Percentage (%)**	**Active Nailbed Changes Cases (N)**	**Active Nailbed Changes Percentage (%)**	**Late Nailbed Changes Cases (N)**	**Late Nailbed Changes Percentage (%)**	**P VALUE**
<10	10	71.43	4	28.57	0	0	<0.001
10-20	0	0	20	95.23	1	4.77	
>20	0	0	6	23.07	20	76.93	

Table 5 shows that low modified Rodnan Score (<10) consists of more Early nailbed changes (71.43%). Scores between 10-20 shows more of Active changes (95.23%) and scores of >20 shows more of Late nailbed changes (76.93%). Nailbed capillaroscopic patterns are related with Modified Rodnan Score which is statistically significant (P <0.05) by Fisher's test.

Figure 4 shows capillaroscopic patterns in various clinical presentations of these patients. Raynaud's phenomenon predominantly showed Active changes (50.87%) in capillaroscopy followed by late changes (33.35%). Active changes were predominant in other findings such as Skin tightening (49.12%) , ILD (51.16%) , Dysphagia (46.66%) and Arthritis (40%). Late changes were predominant in cases of Malignancy (100%).

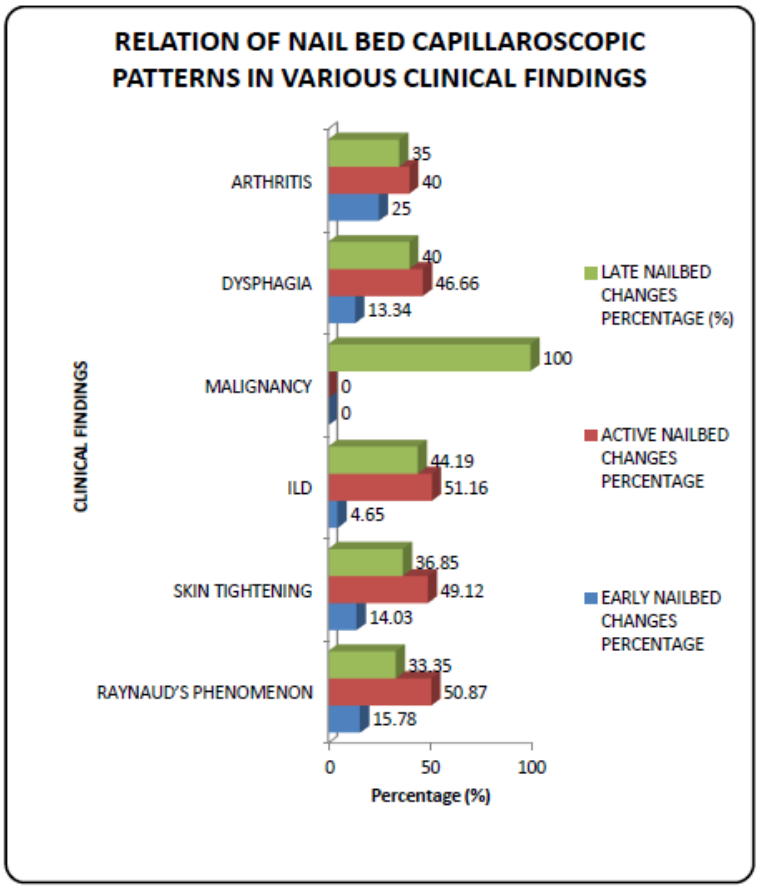

FIGURE 4 : RELATION OF NAILBED CAPILLAROSCOPIC PATTERNS IN VARIOUS CLINICAL FINDINGS

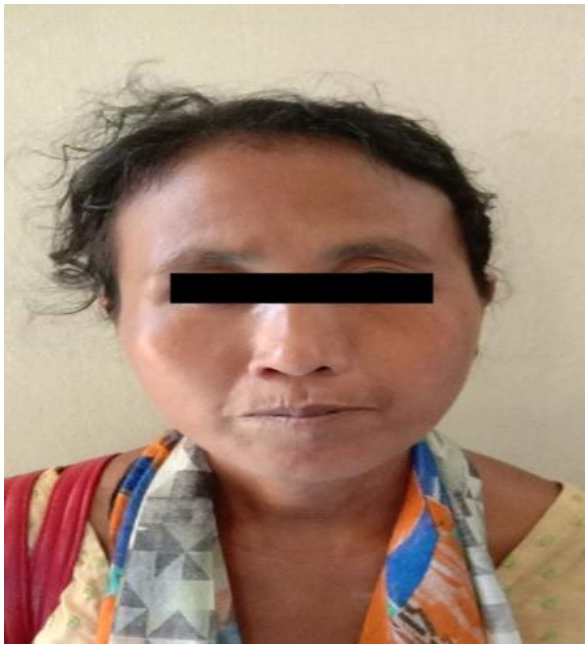

FIGURE 5 : FACIES IN SCLERODERMA

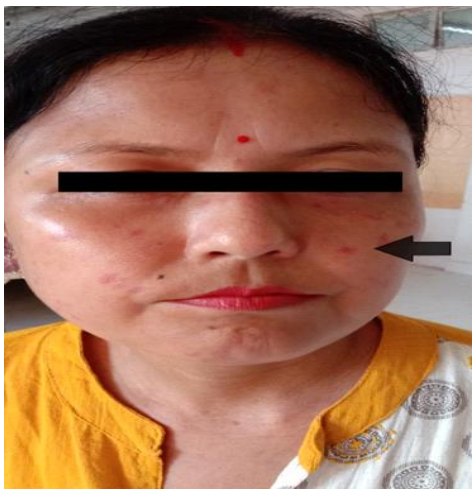

FIGURE 6 : TELANGIECTASIA IN SSC CASE

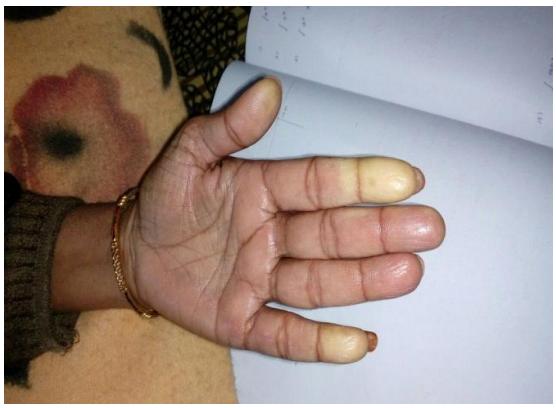

FIGURE 7 : RAYNAUDS PHENOMENON IN ONE OF THE CASES

IV. Discussion

Pulmonary Hypertension was present in 14 out of 61 patients (22.95%) which was common in DcSSC than LcSSC. It is an important prognostic marker in SSC. All the cases (61) have scleroderma pattern on nailfold capillaroscopy in this study. Maximum patients with LcSSc had Active capillaroscopic changes (50%)

and DcSSc cases had a maximum of Active changes (50%) followed by Late capillaroscopic changes (43.75%). Overlap syndrome also showed similar patterns with Active changes (47.36%) being the highest but was followed by Early changes with 31.57%. In a study by P.Caramaschi et. al. thirty-six subjects (34.9%) had an early, 45 (43.7%) an active and 22 (21.4%) a late NVC pattern. Early NVC changes representing microangiopathy in SSc are suggested to be caused by endothelial cell activation, inflammation and production of pro-angiogenic factors, followed by vascular regression and angiostasis . This eventually results in loss of capillaries. A severe NVC pattern is associated with worse disease outcome.[9] A significant association ($p<0.05$) was found between nailfold capillaroscopic findings with PAH and ILD respectively. We found out that the progression of skin, lung, heart and peripheral vascular involvement were all related to the worsening of microangiopathy as directly assessed by NVC. The relation between NVC patterns and clinical manifestations of SSc may be due to common pathogenetic mechanisms, involving microvasculature at different levels and supports the concept that microvessel injury is the pivotal lesion of the complex pathogenesis of the disease. This proves that NVC is not just a diagnostic tool , but is also a prognostic tool in SSC. Caramaschi's study also showed significant relation NVC with ILD.[9] However, a study by Dogan did not find any relation of NVC with ILD.[10] But this study found significant association with both PAH and ILD. Also significant relation of NVC with Modified Rodnan Score was found. Late patterns were consistent with higher Modified Rodnan Score. This finding is similar to studies by Caramaschi and Jérôme Avouac.[9,11]

V. Conclusion

NVC is a cheap and non invasive tool for :

- Early diagnosis of SSC
- Early prediction of complications
- Prompt us to take effective measures to reduce mortality and morbidity.

Our study has also shown its association with vascular, cutaneous as well as systemic manifestations of SSC. While limited research is available in this aspect, various studies are being done lately to see the immense potential of this tool in the field of SSc. It can also be used to see the effectiveness of the drug therapies in these patients. Thus , with the help of Nail fold capillaroscopy , we can diagnose SSc at an early stage and intervene to increase the lifespan of the patients and thereby reduce both mortality and morbidity of such patients.

LIMITATIONS

- Duration of the study is less, that is 1 year. As Systemic Sclerosis cases are not so commonly encountered, increasing the duration of study could have led to inclusion of more cases and an even more elaborate study.
- Pulmonary arterial hypertension was diagnosed using Echocardiography. Right Heart catheterisation is not done in our hospital.

SOURCES OF FUNDS : NIL.
CONFLICT OF INTEREST : NONE

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