ORIGINAL RESEARCH PAPER
Volume-9 | Issue-1 | January-2020 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

NAILFOLD CAPILLAROSCOPIC PROFILE OF CONNECTIVE TISSUE DISEASE – RELATED INTERSTITIAL LUNG DISEASE AT A TERTIARY CARE CENTER IN NORTH INDIA

Rheumatology

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ABSTRACT

BACKGROUND: Lung involvement especially interstitial lung disease (ILD), can be the first manifestation of an underlying connective tissue disorder (CTD), at times preceding the extra-pulmonary features by many years. Nailfold capillaroscopy is an important tool, which helps us in early recognition of microvascular changes in patients with ILD.

METHODS: This is a single center cross-sectional observational study of 50 patients with CTD-ILD. They were classified into 4 main groups : idiopathic inflammatory myositis associated ILD (IIM -ILD), mixed connective tissue disorder associated ILD (MCTD-ILD), primary Sjogren Syndrome associated ILD (pSS-ILD) and Systemic sclerosis associated ILD (SSc-ILD). They were also classified according to radiologic lung patterns on HRCT chest, as UIP pattern or NSIP pattern. Nailfold capillaroscopy (NFC) was performed for all patients at room temperature and various NFC parameters were recorded and analysed using the Kruskal-Wallis non-parametric test and chi-square test wherever applicable.

RESULTS: The mean age of patients was 43.6 ± 14.3 years. Mean duration of the disease was 58.4 ± 20.2 months. There were 32 patients with the UIP pattern and 18 patients with the NSIP pattern of ILD . The commonest NFC abnormalities were megacapillaries and microhemorrhages (20% and 22% respectively). The difference between the mean capillary density was not significant between subgroups (p= 0.337). This was true for other NFC parameters too.

CONCLUSION: This study is one of the first in describing the nailfold capillaroscopic changes in patients of CTD-ILD in the Indian subcontinent.

KEYWORDS

Nailfold Capillaroscopy, Connective Tissue Disorder Related Ild (Ctd-ild), Microvascular Changes

1. INTRODUCTION

Interstitial lung disease (ILD) is a heterogeneous group of parench ymal lung disorders that result from variable etiologies but share common radiologic, pathologic, and clinical manifestations[1]. The exact prevalence and incidence of the interstitial lung disease are unknown. Studies suggest a prevalence of 80.9 per 100,000 for men compared to 67.2 per 100,000 for women in western countries. The overall incidence of interstitial lung disease is slightly more in men (31.5 per 100,000 per year) and increases with age[2].

The exact incidence of ILD in India is not known. A large nationwide study from 27 centers across India by Sheetu Singh et al comprising of 1084 patients with ILD concluded that Hypersensitivity pneumonitis was the most common new onset ILD in India, followed by connective tissue disease related ILD (CTD-ILD) and idiopathic interstitial pneumonia (IIP)[3]. The prevalence of CTD-ILD occupies 19% ~ 34% of ILD as per studies done in western countries[4-5]. However data for CTD-ILD is lacking for the Indian subcontinent.

Microvascular involvement in systemic inflammatory diseases has been well known since the 19th century. Abnormal microangiopathy of nailfold often occurs in systemic rheumatic diseases, especially in scleroderma and related conditions. It is used as a noninvasive, simple, repeatable, highly sensitive and inexpensive method of evaluating microvascular abnormalities in rheumatic diseases [6].

Most of the studies showing specific NFC findings have involved patients with systemic sclerosis, polymyositis, and/or Raynaud's phenomenon[7-11]. But none of these studies show the relation between lung involvement and nailfold changes.

The present study is a small attempt to characterize the nailfold capillaroscopic (NFC) changes associated with CTD - ILD ,and to find the association (if any) with the serological and radiological features.

2. MATERIALS AND METHODS

2.1. PATIENTS :

A total of 50 patients were included in the study. They were classified into 4 main groups: idiopathic inflammatory myositis associated ILD (IIM -ILD), mixed connective tissue disorder associated ILD (MCTD-ILD), primary Sjogren Syndrome associated ILD (pSS-ILD) and Systemic sclerosis associated ILD (SSc-ILD). They were also classified according to radiologic lung patterns on HRCT chest, as UIP pattern or NSIP pattern

All patients in each group had been diagnosed at least 1 year previously and were involved with the study at the time of their NFC study. Their clinical, laboratory, radiologic, and functional data were obtained from medical records. At the time of their clinical visit for the study, additional demographic data, complaints, and the results of current physical examinations were also recorded.

Nailfold capillaroscopy was performed on all patients. None of them were in an acute phase of pulmonary disease or taking vasoactive drugs. Patients suffering from peripheral microangiopathies -such as diabetes, hypertension, or recent trauma-that could potentially modify the capillaroscopic findings were excluded.

All tests were performed and subsequently analyzed by two independent observers who had no knowledge about the patient's diagnosis. Appropriate informed consent was obtained from each patient and the study was approved by the Institutional Ethics Committee.

2.2. NAILFOLD CAPILLAROSCOPY AND IMAGE ANALYSIS :

NFC was performed at room temperature (between 20-22°C) with the patient kept inside in a seated position with the hand being examined placed at heart level for at least 15 minutes before the exam. One drop of vegetable oil was applied to the nailfold to maximize the translucency of the keratin layer. Capillary tests were performed on 2 fingers of each hand (4th and 5th digits,) For each finger, two images (from right and from left side of median line) were captured. NFC was performed using a computerized video-capillaroscopy system. Images were subsequently captured, coded, stored, and analyzed later by two independent observers.

For each capillaroscopic image, the following parameters were

microhemorrhages, bushy capillaries and neo-angiogenesis. "Mega capillary" is used to describe the situation when the magnitude of a capillary is wider than 0.05 micrometers. Micro-hemorrhages are defined as the presence of 2 or more bleeding areas in at least 2 fingers. Neoangiogenesis, or neoformation, is a highly tortuous and arborized capillary loop cluster, often surrounded by a dropout of normal capillary loops. Loops with limbs that originate from multiple small buds are labelled "bushy."

2.3 STATISTICAL ANALYSIS.

The mean and SD of all examined fingers were calculated for quantitative capillaroscopic parameters in each patient. To detect differences between the four groups, the Kruskal-Wallis non-parametric test and chi-square test were used when applicable. A p value ≤ 0.05 was considered significant.

3. RESULTS

We performed NFC on 50 patients with CTD-associated ILD (5 IIM-ILD, 23 MCTD-ILD, 7 pSS- ILD and 15 SSc-ILD). We analyzed the differences in morphological capillaroscopic parameters between the groups. Table 1 summarizes the clinical and demographic characteristics of patients in each group. Most of the patients were women in all the groups. The mean age of patients was 43.6 ± 14.3 (min. 42, max. 65 years). Between the subgroups' ages there was no significant difference. Most of the patients were nonsmokers (47, 94.0%). Only 2 (4%) patients were former smokers; 1 (2%) patient was a current smoker. The current smoker was a case of MCTD-ILD while former smokers were patients of SSc-ILD.

Mean duration of the disease was 58.4 ± 20.2 months (min. 20, max. 98 months). For disease duration there was no statistically significant difference between the subgroups. There were 32 patients with the UIP pattern and 18 patients with the NSIP pattern of ILD on HRCT Chest.

Table 1 : Demographic, clinical and radiological features of CTD-ILD patients

Parameters	IIM- ILD	MCTD-ILD	pSS-ILD	SSc-ILD	Total
Number (%)	5 (10)	23 (46)	7 (14)	15 (30)	50
Gender (M/F)	1/ 4	4/19	0/7	3/12	8/42
Age (mean ± SD)	55.6 ± 8.6	37.3±12.9	51.3±13.3	45.4±14.5	43.6±14.3
Smoker, (n, %)	0	1 (4.3)	0	2 (13.3)	3 (6)
Duration of disease, mean ± SD (months)	50± 21.2	61± 23.1	66± 16.9	53.7± 16.1	58.4±20.2
UIP (n, %)	5(100)	11 (47.8)	4 (57.1)	11 (73.3)	32 (64)
NSIP	0	12 (52.2)	3 (42.9)	4 (26.7)	18 (36)
FVC (% predicted)	63.3±12.6	71.3±10.96	60.8±14.8	63.7±13.2	66.7±12.7
DLCO SB (% predicted)	61.6±6.8	70.9±15.8	65.8±11.4	53.4±12.8	63.8±15.4
SpO2 (%)	95.0±2.3	94.6±1.7	92.8±0.7	95.4±1.6	95.5±1.4

Between pulmonary function test parameters there were significant differences only in diffusion capacity (DLCO SB) between subgroups. DLCO SB was lower in the SSc-ILD group compared to the other subgroups (p= 0.004).

The common autoantibodies detected were Anti Jo-1 in IIM-ILD (4, 80%), Anti RNP in MCTD-ILD (23, 100%), Anti Ro60/52 in pSS – ILD (6, 85.7%) and Anti Scl-70 in SSc-ILD(15, 94%) subgroups.

3.1 CAPILLAROSCOPIC FINDINGS

The mean capillary density was 6.24 ± 0.68 / mm (range 5-8). Between subgroups, mean capillary density was 5.8 loops/mm in IIM-ILD patients; 6.34 loops/mm in MCTD-ILD; 6.42 loops/mm in pSS-ILD and 6.13 loops/mm in the SSc-ILD group (Table 2).

The difference between the mean capillary density was not significant between subgroups (p= 0.337). This was true for other NFC parameters too (capillary length, capillary width and inter-capillary distance).

Table 2 : Nailfold capillaroscopy parameters in CTD-ILD subgroups

NFC parameters	IIM- ILD	MCTD-ILD	pSS-ILD	SSc-ILD	Total	P value
Capillary density	5.8 ± 0.44	6.34 ± 0.57	6.42 ± 1.13	6.13 ± 0.63	6.24 ± 0.68	0.327
Capillary length	244.60 ± 15.12	245.30 ± 10.6	247.42 ± 10.80	242.13 ± 9.89	244.58 ± 10.71	0.722
Capillary width	46.28 ± 2.58	47.34 ± 1.79	47.42 ± 1.98	46.6 ± 1.88	47.02 ± 1.92	0.467
Intercapillary distance	114.8 ± 4.88	112.52 ± 9.68	115.57 ± 2.57	112.86 ± 9.02	113.28 ± 8.33	0.829

evaluated: capillary density (number of capillaries/mm), capillary length, capillary width and intercapillary distance (ICD) (all in microns).

Abnormal morphologies of capillaries were described as megaca pillaries, The abnormal capillary morphologies detected were megacapillaries, microhemorrhages, bushy capillaries and neo-angiogenesis. The commonest abnormalities were megacapillaries and microhem orrhages (20% and 22% respectively).

Bushy capillaries were commonly seen in MCTD-ILD group (9,40 %) and neo-angiogenesis was seen in few patients with MCTD –ILD and IIM-ILD.

DISCUSSION

Nailfold Capillaroscopy is a non-invasive diagnostic method used for looking at microcirculation. Peripheral microangiopathy can be detected by NFC at early stages of disease. Between CTDs, NFC findings give typical information, especially in scleroderma, dermato myositis, mixed connective tissue disease, and undiffe rent iated connective tissue disease- all are called as "sclerod erma-like pattern."

ILD can be the first presenting finding in CTDs. Before accepting IIP as an undefined ILD, NFC should be performed on this group of patients[12]. Also, it is recognized that there is a need to provide a clinical algorithm for classifying and managing IIP cases. This is particularly applicable when no biopsy is available and high-resolution computed tomography is not diagnostic[13]. In our study we intended to discover whether NFC findings could be a clue for detecting early forms of CTD-ILD.

The first result of this study is the finding that capillaroscopic alterations are more common in the CTD- ILD group. Mean capillary density was significantly reduced in all the subgroups. In sub-group analysis, the common annormal morphologies encountered were microhemorrhages, megacapillaries and bushy forms. Patients of MCTD-ILD had the maximum number of abnormal morphologies on NFC.

Changes in microcirculation are thought to be a result of an imbalance between angiogenic and angiostatic factors. Also, the prevalence of a high anti-endothelial cell antibody (AECA) has been frequently associated with vascular lesions and activity of autoimmune diseases[7,14].

There is only one study that compares the NFC findings in IPF patients as mentioned above, and they hypothesized that capillary changes could be a con- sequence of systemic endothelial dysfunction, similar to other CTDs but a less pronounced form. The predicted cause was an imbalance between angiogenic and anti-angiogenic cytokines, such as vascular endothelial growth factor (VEGF), IL-8, and endothelin-1[15].

There is no study in the literature that evaluates NFC findings of CTD-ILD patients in India. Our study, is a small step towards recognition and characterization of NFC changes in patients with CTD-ILD.

CONCLUSION

This study is one of the first in describing the nailfold capillaroscopic changes in patients of CTD-ILD in the Indian subcontinent. We found that patients of CTD-ILD had more prevalence of abnormal morphologies on NFC as compared to IIP. Nailfold capillaroscopy is a non-invasive tool to detect early features of CTD related ILD in a

cohort of patients with IIP. However, a limitation of the current study is the small number of patients in each group; therefore, it is difficult to make strong associations between groups. Additional studies are needed to better define the exact role of nailfold capillaroscopy in the diagnostic procedure of ILD

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