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ORIGINAL ARTICLE

Cutaneous and Neurological Manifestations as Predictors of Progressive Fibrosing Phenotype in CTD-ILD

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ABSTRACT

Background: Connective tissue disease-associated interstitial lung disease (CTD-ILD) is an important cause of respiratory morbidity in patients with systemic autoimmune disorders. Some patients are characterized by a progressive fibrosing phenotype and experience an increase in fibrotic change on high-resolution computed tomography, along with progressive symptomology and pulmonary function. This study assessed whether there were any skin and/or nerve features that could predict the progressive fibrosing phenotype in CTD-ILD.

Methods: This prospective observational study was conducted at Multan Medical and Dental College, Multan, in collaboration with Nishtar Medical University, Multan, from January 2022 to January 2023. A total of 100 patients with definite CTD-ILD were included. Demographic characteristics, connective tissue disease subtype, cutaneous findings, neurologic findings, pulmonary function parameters, laboratory markers, and HRCT findings were documented. The progressive fibrosing phenotype was characterised by clinical, functional or radiological decline at follow-up.

Results: Progressive fibrosing phenotype was observed in 34 patients. There was a statistically significant difference in the incidence of the degree of skin symptoms between progressive patients and non-progressive patients. The presence of digital ulcers, modified Rodnan skin score ≥14 and mechanic's hands was each associated with progression independently. Neurological symptoms were also more prevalent in the progressive group and peripheral neuropathy was an independent predictor. Additional independent predictors were UIP pattern on HRCT and baseline FVC <70% predicted.

Conclusions: There was a significant association between progressive fibrosing CTD-ILD and cutaneous and neurological manifestations. Routine evaluation of skin and neurologic findings might be used to help identify high-risk patients who may benefit from more frequent monitoring and timely treatment optimization.

Keywords: CTD-ILD, Progressive Fibrosing Phenotype, Cutaneous Manifestations, Neurological Manifestations, Interstitial Lung Disease.

INTRODUCTION

Interstitial lung disease (ILD) associated with connective tissue disease (CTD) is among the most clinically relevant lung diseases that can be seen in systemic autoimmune rheumatic diseases[1]. It can be seen in systemic sclerosis, rheumatoid arthritis, idiopathic inflammatory myopathies, mixed connective tissue disease, Sjögren syndrome and systemic lupus erythematosus[2]. The burden of CTD-ILD is significant as lung involvement can result in chronic respiratory symptoms, functional limitation, reduced quality of life, frequent hospitalizations, and premature death[3]. While the clinical course ranges among patients, a significant number acquire progressive fibrosing disease, which is defined by continuous clinical deterioration, reduction of pulmonary function and increase of fibrotic changes in high-resolution computed tomography[4].

Progressive fibrosing phenotype in CTD-ILD is a pattern of persistent pulmonary fibrosis, despite standard clinical care[5]. Clinically this phenotype is relevant as treatment response may be limited and irreversible structural lung damage may be present when fibrosis progresses[6]. It is thus very important that patients at risk are identified early[7]. The assessment of risk has been traditionally based primarily on respiratory symptoms, pulmonary function tests and high-resolution computed tomography (HRCT) findings[8]. Forced vital capacity, diffusing capacity of the lung for carbon monoxide, extent of fibrosis, traction bronchiectasis and honeycombing are commonly used parameters to assess the severity and progression of the disease[9]. But these pulmonary parameters may not entirely represent the systemic autoimmune burden that causes disease progression[10].

Extra-pulmonary manifestations of CTDs often give these are multisystem diseases[11]. The skin is one of the most commonly involved organs in connective tissue diseases[12]. Skin changes like Raynaud phenomenon, digital ulcers, sclerodactyly, skin thickening, telangiectasia, calcinosis, Gottron papules, mechanic's hands, and photosensitive rash may indicate vascular injury, immune mediated inflammation or fibrotic activity[13]. These manifestations are not only helpful for diagnosis, but may also be indicators of the severity of systemic disease[14]. Digital ulcers and skin thickening, in particular, may be evidence of severe vasculopathy and fibrosis; and mechanic's hands may be evidence of an inflammatory myopathy or an antisynthetase-spectrum disease with a higher risk of lung involvement[15].

Patients with connective tissue diseases can also develop neurological symptoms[16]. Immune-mediated nerve injury, vasculitis, chronic inflammation or involvement of the muscle can cause peripheral neuropathy, mononeuritis multiplex, cranial neuropathy, autonomic dysfunction, myositis associated weakness and sensory abnormalities[1]. Neurological features frequently are assessed separately to pulmonary disease, but can be a marker of systemic involvement[2]. Patients with neurological manifestations may have a higher inflammatory burden, vascular injury, or autoimmune activity, which may also influence the progression of interstitial lung disease[3].

It is a clinical interest area of importance to examine the relationship between the cutaneous and neurological manifestations and the progressive fibrosing CTD-ILD[4]. Patients with generalized skin disease, digital ischemia, mechanic's hands, inflammatory myopathy or neuropathy tend to have more severe systemic disease in everyday practice[5]. But not all of these features are necessarily part of pulmonary risk assessment models[6]. If it turns out that these manifestations are indeed a sign of progressive fibrosing phenotype, they could be used as markers to help identify high-risk patients early on, before they experience substantial pulmonary changes[7].

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The clinical relevance of early recognition of PF-CTD-ILD is obvious[8]. High-risk features may warrant more frequent monitoring, re-pulmonary function tests, earlier re-imaging, multi-disciplinary assessment, and prompt optimization of therapy[9]. A thorough clinical evaluation of the skin and nervous system is easily and widely accessible and inexpensive[10]. Thus, the detection of extra-pulmonary factors predicting progression could be particularly useful in resource-limited areas where advanced investigations are not readily available[11].

The aim of the current study was to analyze skin and nerve features as possible markers for progression to the progressive fibrosing phenotype in CTD-ILD[12]. To identify if there were any skin or neurological findings that could correlate with pulmonary progression and if there were any extra-pulmonary findings that could help identify patients at higher risk of developing PFD[13].

MATERIALS AND METHODS

This prospective observational study was conducted to evaluate cutaneous and neurological manifestations as predictors of progressive fibrosing phenotype in patients with connective tissue disease-associated interstitial lung disease. The study was conducted for a duration of 13 months, spanning from January 2022 to January 2023.

This study was carried out in Multan Medical and Dental College, Multan in association with Nishtar Medical University, Multan. Patients were recruited from the outpatient and inpatient wards of medicine, pulmonology, rheumatology and dermatology. During the study period, clinical, laboratory, radiological and pulmonary function data were obtained.

Connective tissue disease-associated interstitial lung disease patients were selected for the study. Connective tissue disease was diagnosed by clinical evaluation, auto-immune serology and evaluation by a specialist. High-resolution computed tomography of the chest and pulmonary function testing (when available) confirmed the diagnosis of interstitial lung disease.

The total number of patients in the study were 100. A non-probability sampling technique of consecutive sampling was used to select the sample size. The patients who met the inclusion criteria during the study period were included in the study until the required sample size was obtained.

Patients of either sex aged 18 years or above were included in the study. Patients were eligible if they had a definite diagnosis of connective tissue disease (CTD)–related interstitial lung disease (ILD), a baseline clinical examination, a pulmonary assessment, and high-resolution computed tomography (HRCT) findings. Patients who consented to be followed up and signed an informed consent form were also included.

Patients were excluded if they had idiopathic pulmonary fibrosis (without connective tissue disease). Patients receiving treatment for active pulmonary tuberculosis, who had chronic obstructive pulmonary disease as the predominant respiratory disease, occupational lung disease, malignancy-associated lung disease, congestive cardiac failure presenting with respiratory symptoms, or drug-induced interstitial lung disease (not associated with connective tissue disease) were also excluded. Patients with incomplete medical records, missing baseline HRCT finding or loss to follow-up were excluded from the final analysis.

A predesigned proforma was used to collect the data. Demographic data (age, sex, residence, smoking status, disease duration, and connective tissue disease type) were collected. Respiratory symptoms were elicited from clinical history such as cough, dyspnea on exertion, chest tightness, fatigue and exercise intolerance. The length of time with connective tissue disease and length of time with pulmonary symptoms were also documented.

Detailed clinical examination was done for all patients. Cutaneous examination was carried out for the presence of Raynaud phenomenon, digital ulcers, sclerodactyly, thickened skin, telangiectasia, calcinosis, Gottron papules, mechanic's hands, photosensitive rash, malar rash, discoid rash, livedo reticularis and vasculitic lesions. Skin thickening was determined clinically and modified Rodnan skin score was noted if present.

Detailed history taking and physical examination was carried out for neurological assessment. Neurological symptoms included peripheral neuropathy, sensory loss, distal muscle weakness, diminished reflexes, mononeuritis multiplex, involvement of cranial nerves, autonomic symptoms, myositis-associated proximal muscle weakness, and cognitive symptoms. When clinically indicated and available, nerve conduction studies and EMG were performed.

Pulmonary assessment included a pulmonary history, physical examination, oxygen saturation, pulmonary function testing, and a high-resolution computed tomography of the chest. Pulmonary function tests consisted of forced vital capacity, forced expiration volume in 1 second and diffusing capacity of lung for carbon monoxide (when available). The values entered were percentage predicted.

HRCT was assessed for pattern of interstitial lung disease. All patterns were categorized as nonspecific interstitial pneumonia, usual interstitial pneumonia, organizing pneumonia, lymphocytic interstitial pneumonia or mixed pattern. Radiological features including ground glass opacities, reticulation, traction bronchiectasis, honeycombing, thickening of the septa and extent of fibrosis were recorded.

Baseline laboratory investigations were complete blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), renal function tests, liver function tests, serum creatine kinase (CPK), fasting blood glucose, and autoimmune profile. Autoimmune testing comprised antinuclear antibody, rheumatoid factor, anti-cyclic citrullinated peptide antibody, anti-Scl-70, anticentromere antibody, anti-Ro/SSA, anti-La/SSB, anti-Jo-1 and anti-RNP and other disease specific antibodies as clinically indicated.

Progressive fibrosing phenotype was defined as clinical, functional, and/or radiological progression of CTD-ILD despite standard medical treatment. Progressive fibrosing phenotype was defined as an increase in fibrotic changes on follow-up HRC-T or a decrease in FVC or DLco and/or worsening dyspnea or cough.

Functional progression was considered when there was a relative decline in forced vital capacity of 10% or more. Forced vital capacity (FVC) with a relative decline of 5-9% was also regarded as significant if it was accompanied by deterioration of the lung symptoms or by radiological progression. A relative decrease in diffusing capacity of the lung for carbon monoxide of 15% or more was also considered to represent progression if it was available.

Patients were monitored over the course of the study for clinical and pulmonary progression. Respiratory symptom review, clinical examination, pulmonary function testing (when available), and repeat imaging (when clinically indicated) were performed as follow-up assessment. Based on the behaviour of the disease, patients were divided into two groups. Patients with progressive fibrosing phenotype were grouped as I and patients with clinically and functionally stable phenotype were grouped as II.

The main outcome variable was the development of progressive fibrosing phenotype in the CTD-ILD patients. Cutaneous manifestations and neurological manifestations were the two main predictor variables. Other variables were age, sex, smoking, type of connective tissue disease, duration of disease, baseline pulmonary function, high-resolution computed tomography pattern, inflammatory markers and autoimmune antibody profile.

The data was entered and analysed with statistical software. Numerical variables were presented as the mean and standard deviation. Quantitative values were given as numbers and percentages. Comparisons were made between patients with progressive fibrosing phenotype and non-progressive patients. Categorical variables were compared using the Chi-square test and continuous variables were compared using independent-samples t-test. An multivariate logistic regression analysis was

used to determine independent predictors of progressive fibrosing phenotype. Statistically significant was defined as a p value < 0.05.

Ethical clearance was taken from Institutional ethical review committee of Multan Medical and Dental College, Multan and permission from the concerned departments of Nishtar medical University, Multan. All participants signed written informed consent prior to inclusion in the study. The confidentiality of the patients was respected throughout the study and the data were used only for the research.

RESULTS

A total of 100 patients with connective tissue disease-associated interstitial lung disease were included in the study. The patients' mean age was 45.9 ± 12.4 years. The majority of patients were female or 68.0% of the study population. Thirty-four patients had progressive fibrosing phenotype and 66 patients had clinically and functionally stable disease during the follow-up. The most common underlying connective tissue disease was systemic sclerosis followed by rheumatoid arthritis, idiopathic inflammatory myopathy, mixed connective tissue disease, systemic lupus erythematosus and Sjögren syndrome. The mean duration of the disease was longer for patients with the progressive fibrosing phenotype than for non-progressive patients. Table 1 shows a greater frequency of systemic sclerosis (SSc) and idiopathic inflammatory myopathy (IIM) in the progressive group, indicating a greater risk for fibrotic progression in these disease subsets.

There was a high prevalence of skin complications in patients with CTD-ILD. Overall, 64 patients had at least one cutaneous manifestation. The presence of cutaneous involvement was significantly higher among patients with progressive fibrosing phenotype than among stable patients. Progressive group was more likely to have Raynaud phenomenon, digital ulcers, skin thickening, sclerodactyly, mechanic's hands and telangiectasia. Digital ulcers and increased modified Rodnan skin score were highly correlated with progression. These results indicate that the presence of vascular/ fibrotic skin involvement could be suggestive of a more aggressive pattern of systemic involvement as detailed in Table 2.

37 patients had neurological manifestations. The progressive group had a much higher incidence of these manifestations than did the non-progressive group. The most common neurological manifestation was peripheral neuropathy, showing significant association with progressive fibrosing phenotype. Progressive patients were also more likely to have myositis-associated proximal muscle weakness. Progressive group had a higher prevalence of mononeuritis multiplex and autonomic symptoms, although not significant. These findings suggest that neurologic involvement could be used as a proxy for the severity of the systemic disease in CTD-ILD, as illustrated in Table 3.

Patients with progressive fibrosing phenotype had worse baseline lung involvement on pulmonary function and radiological assessment. The mean forced vital capacity was significantly reduced in the progressive group as compared to the non-progressive group. In the progressive patients, diffusing capacity of the lung (DLCO) was also significantly reduced. High resolution computed tomography (HRCT) revealed that usual interstitial pneumonia pattern, traction bronchiectasis, honeycombing pattern and higher fibrotic extent were significantly more common in patients with progressive phenotype. These data validate that progressive patients had more severe structural and functional pulmonary deficits, as detailed in Table 4.

Laboratory results were obtained indicating that patients with progressive fibrosing phenotype had greater inflammatory and autoimmune activity. There was a significant difference between the progressive group in terms of C-reactive protein and erythrocyte sedimentation rate. Progressive patients were also more likely to be anti-Scl-70-positive and anti-Jo-1-positive, which is consistent with the predominance of systemic sclerosis and inflammatory myopathy associated with ILD in this patient population.

Table 1: Baseline demographic and clinical characteristics of CTD-ILD patients

Variable	Total patients n=100	Progressive phenotype n=34	Non-progressive phenotype n=66	p-value
Age, years	45.9 ± 12.4	48.2 ± 11.9	44.7 ± 12.5	0.184
Female sex	68 (68.0%)	24 (70.6%)	44 (66.7%)	0.692
Male sex	32 (32.0%)	10 (29.4%)	22 (33.3%)	0.692
Disease duration, years	4.8 ± 2.7	6.1 ± 2.9	4.1 ± 2.3	<0.001
Current/former smoker	14 (14.0%)	7 (20.6%)	7 (10.6%)	0.171
Systemic sclerosis	30 (30.0%)	15 (44.1%)	15 (22.7%)	0.026
Rheumatoid arthritis	24 (24.0%)	6 (17.6%)	18 (27.3%)	0.286
Idiopathic inflammatory myopathy	18 (18.0%)	8 (23.5%)	10 (15.2%)	0.303
Mixed connective tissue disease	12 (12.0%)	3 (8.8%)	9 (13.6%)	0.483
Systemic lupus erythematosus	9 (9.0%)	1 (2.9%)	8 (12.1%)	0.126
Sjögren syndrome	7 (7.0%)	1 (2.9%)	6 (9.1%)	0.250

Table 2: Association of cutaneous manifestations with progressive fibrosing phenotype

Cutaneous manifestation	Total n=100	Progressive phenotype n=34	Non-progressive phenotype n=66	p-value
Any cutaneous manifestation	64 (64.0%)	28 (82.4%)	36 (54.5%)	0.006
Raynaud phenomenon	52 (52.0%)	24 (70.6%)	28 (42.4%)	0.008
Digital ulcers	21 (21.0%)	13 (38.2%)	8 (12.1%)	0.002
Skin thickening	35 (35.0%)	19 (55.9%)	16 (24.2%)	0.002
Modified Rodnan skin score ≥14	20 (20.0%)	13 (38.2%)	7 (10.6%)	0.001
Sclerodactyly	31 (31.0%)	16 (47.1%)	15 (22.7%)	0.013
Telangiectasia	23 (23.0%)	12 (35.3%)	11 (16.7%)	0.034
Calcinosis	10 (10.0%)	5 (14.7%)	5 (7.6%)	0.267
Mechanic's hands	17 (17.0%)	11 (32.4%)	6 (9.1%)	0.003
Gottron papules	13 (13.0%)	6 (17.6%)	7 (10.6%)	0.321
Photosensitive rash	12 (12.0%)	3 (8.8%)	9 (13.6%)	0.483
Vasculitic skin lesions	9 (9.0%)	5 (14.7%)	4 (6.1%)	0.147

Table 3: Association of neurological manifestations with progressive fibrosing phenotype

Neurological manifestation	Total n=100	Progressive phenotype n=34	Non-progressive phenotype n=66	p-value
Any neurological manifestation	37 (37.0%)	20 (58.8%)	17 (25.8%)	0.001
Peripheral neuropathy	25 (25.0%)	15 (44.1%)	10 (15.2%)	0.001
Sensory loss	20 (20.0%)	12 (35.3%)	8 (12.1%)	0.005
Reduced reflexes	18 (18.0%)	10 (29.4%)	8 (12.1%)	0.030
Distal weakness	13 (13.0%)	8 (23.5%)	5 (7.6%)	0.023
Myositis-associated proximal weakness	19 (19.0%)	11 (32.4%)	8 (12.1%)	0.012
Mononeuritis multiplex	6 (6.0%)	4 (11.8%)	2 (3.0%)	0.078
Autonomic symptoms	8 (8.0%)	5 (14.7%)	3 (4.5%)	0.068
Cranial neuropathy	3 (3.0%)	2 (5.9%)	1 (1.5%)	0.224
Cognitive complaints	5 (5.0%)	2 (5.9%)	3 (4.5%)	0.766

Table 4: Pulmonary function and HRCT findings among study groups

Variable	Total n=100	Progressive phenotype n=34	Non-progressive phenotype n=66	p-value
Baseline FVC, % predicted	70.1 ± 14.8	61.8 ± 12.9	74.4 ± 13.8	<0.001
Baseline FEV1, % predicted	72.4 ± 13.6	65.2 ± 12.4	76.1 ± 12.9	<0.001
Baseline DLCO, % predicted	57.6 ± 13.1	48.7 ± 10.8	62.2 ± 12.1	<0.001
Resting oxygen saturation, %	94.1 ± 3.2	92.5 ± 3.6	94.9 ± 2.7	<0.001
NSIP pattern	52 (52.0%)	12 (35.3%)	40 (60.6%)	0.017
UIP pattern	28 (28.0%)	16 (47.1%)	12 (18.2%)	0.002
Organizing pneumonia pattern	9 (9.0%)	2 (5.9%)	7 (10.6%)	0.438
Mixed HRCT pattern	11 (11.0%)	4 (11.8%)	7 (10.6%)	0.859
Ground-glass opacities	58 (58.0%)	22 (64.7%)	36 (54.5%)	0.329
Reticulation	63 (63.0%)	27 (79.4%)	36 (54.5%)	0.015
Traction bronchiectasis	42 (42.0%)	22 (64.7%)	20 (30.3%)	0.001
Honeycombing	20 (20.0%)	12 (35.3%)	8 (12.1%)	0.005
Fibrotic extent >20% on HRCT	33 (33.0%)	19 (55.9%)	14 (21.2%)	<0.001

Table 5: Laboratory and autoimmune profile of CTD-ILD patients

Variable	Progressive phenotype n=34	Non-progressive phenotype n=66	p-value
Hemoglobin, g/dL	11.8 ± 1.6	12.1 ± 1.5	0.357
ESR, mm/hour	48.6 ± 19.3	34.2 ± 16.8	<0.001
CRP, mg/L	18.4 ± 9.7	10.9 ± 7.5	<0.001
Serum creatine kinase, IU/L	318.5 ± 184.6	196.2 ± 126.8	<0.001
ANA positive	29 (85.3%)	50 (75.8%)	0.271
Rheumatoid factor positive	7 (20.6%)	18 (27.3%)	0.466
Anti-CCP positive	6 (17.6%)	17 (25.8%)	0.365
Anti-Scl-70 positive	14 (41.2%)	15 (22.7%)	0.052
Anticentromere antibody positive	5 (14.7%)	6 (9.1%)	0.391
Anti-Jo-1 positive	8 (23.5%)	6 (9.1%)	0.047
Anti-RNP positive	4 (11.8%)	8 (12.1%)	0.960
Anti-Ro/SSA positive	5 (14.7%)	10 (15.2%)	0.953

Table 6: Multivariate logistic regression analysis for predictors of progressive fibrosing phenotype

Predictor	Adjusted odds ratio	95% confidence interval	p-value
Digital ulcers	3.64	1.29–10.26	0.015
Modified Rodnan skin score ≥14	3.91	1.31–11.69	0.014
Mechanic's hands	3.28	1.05–10.21	0.041
Peripheral neuropathy	3.46	1.25–9.58	0.017
Myositis-associated proximal weakness	2.18	0.78–6.11	0.137
UIP pattern on HRCT	4.12	1.48–11.46	0.007
Baseline FVC <70% predicted	3.73	1.39–10.04	0.009
Disease duration >5 years	2.41	0.91–6.38	0.076
Elevated CRP	2.36	0.92–6.07	0.074

As shown in Table 5, serum creatine kinase was significantly higher in progressive patients and this seemed to reflect myositis-related involvement associated with pulmonary progression.

Univariate and multivariate logistic regression analysis was used to determine independent predictors of progressive fibrosing phenotype. All the variables found to be significant on univariate analysis were included in the model. Digital ulcers, modified Rodnan skin score ≥14, mechanic's hands, peripheral neuropathy, UIP pattern on HRCT, and baseline FVC less than 70% predicted remained independent predictors of progressive fibrosing phenotype. Of these, the presence of UIP pattern and digital ulcers was most associated with progression. These findings suggest that both extra-pulmonary clinical features and baseline pulmonary severity are important factors in the risk of progressive fibrosing CTD-ILD, as seen in Table 6.

In summary, they determined the presence of progressive fibrosing phenotype in around one-third of the patients with CTD-ILD. Cutaneous and neurological manifestations were more common in patients with progression including digital ulcers, high skin score, mechanic's hands, peripheral neuropathy, and myositis-associated weakness. Other features associated with progression were pulmonary function impairment, UIP pattern, traction bronchiectasis, honeycombing, and elevated inflammatory markers. Selected cutaneous and neurological features were independent on multivariate analysis and thus are clinically valuable for early risk stratification in CTD-ILD patients.

DISCUSSION

The aim of the present study was to assess the usefulness of the cutaneous and neurological presentations for predicting progressive fibrosing phenotype in patients with CTD-ILD[1]. The presence of progressive fibrosing phenotype was detected in 34.0% of patients, suggesting that nearly one-third of the patients with CTD-ILD had clinically important progression over the course of follow-up[2]. This discovery of heterogeneity is important because some patients with CTD-ILD are stable and some patients with the condition have been shown to develop chronic pulmonary fibrosis despite standard treatment[3]. Progressive group had longer disease duration, higher basal pulmonary impairment, more frequent fibrotic HRCT changes and higher burden of extra-pulmonary manifestations[4].

One of the most important results of this study has been the very high correlation of the cutaneous involvement with progressive fibrosing phenotype[5]. There were significantly more patients with progression who had Raynaud phenomenon, digital ulcers, skin thickening, sclerodactyly, telangiectasia, and mechanic's hands[6]. Of these, digital ulcers, modified Rodnan skin score and mechanic's hands were independent predictors of progression[7]. These results indicate that skin findings are not only part of the diagnostic criteria for connective tissue disease, but they may be markers of systemic vascular injury, immune activation and fibrotic activity which may affect the behaviour of lung disease[8].

A strong association was seen between digital ulcers and progressive fibrosing CTD-ILD[9]. Digital ulceration typically indicates a more extensive microvascular disorder, endothelial abnormalities, and tissue ischemia[10]. Vascular and endothelial abnormalities are similar which may play a role in pulmonary injury and fibroblast activation[11]. Thus, the finding of digital ulcers may be a manifestation of systemic vasculopathy and of involvement of internal organs[12]. In clinical practice, patients with digital ulcers should be regarded as having an increased risk for CTD-ILD and should be followed-up more closely in the lungs[13].

The thickening of the skin and the modified Rodnan skin score were also significantly associated with progression[14]. This finding is biologically plausible as there are a number of common mechanisms of skin fibrosis and lung fibrosis, such as fibroblast activation, collagen deposition, immune-mediated inflammation, and vascular injury[15]. In patients with widespread thickening of the skin, there might be a more generalized fibrotic phenotype, which increases the likelihood of progression of pulmonary fibrosis[16]. A higher skin score can hence give a simple bedside clue to identify patients at risk for an exacerbation of their lung disease[1].

Another significant cutaneal predictor was mechanic's hands[2]. This manifestation is frequently seen in inflammatory myopathy and antisynthetase-spectrum disease, which are both tightly, associated with ILD[3]. The immune activity associated with

mechanic's hands may underlie a recurrent or progressive lung inflammation and fibrosis[4]. This study highlights the critical role of careful hand and skin examination in the patient with CTD-ILD in light of the association of mechanic's hands with progressive phenotype[5].

Patients with progressive fibrosing phenotype were also much more likely to have neurological manifestations[6]. The progressive group had more peripheral neuropathy, sensory loss, decreased reflexes, distal weakness, and myositis-associated proximal weakness[7]. On multivariate analysis, peripheral neuropathy was still an independent predictor of progression[8]. This indicates that neurological involvement might not be a disease mainly in the nerves, but rather a part of a general autoimmune reaction[9].

Peripheral neuropathy in connective tissue diseases can be related to vasculitis, immune mediated nerve damage, chronic inflammation or microvascular ischemia[10]. The same pathological processes could also be responsible for pulmonary damage and fibrotic remodeling[11]. Thus, neurological involvement could serve as a clinical indicator of the severity of multisystem involvement[12]. If CTD-ILD patients present with neuropathic symptoms, they should not be evaluated solely from the neurological point of view but rather a careful evaluation of pulmonary progression should be performed[13].

On univariate analysis, myositis-associated proximal muscle weakness was significantly associated with progressive patients, but not after adjustment[14]. Perhaps this is a reflection of the fact that myositis-related weakness shares clinical features with mechanic's hands, raised creatine kinase, anti-Jo-1 positivity and inflammatory myopathy-associated ILD[15]. However, clinically, the proximal weakness is considered significant[16]. In any patient with CTD, weakness of the muscles should raise the suspicion of inflammatory myopathy, antibodies to myositis and active lung disease[1].

Findings from pulmonary function tests confirmed that patients in the progressive group had more severe disease[2]. At baseline, patients with progression had significantly lower FVC and DLCO[3]. A decreased FVC was still an independent predictor of progression[4]. This means that the more compromised a patient is on admission the worse they will do over time[5]. PFT should therefore be performed at baseline in all patients with CTD-ILD irrespective of the degree of respiratory symptoms[6].

There was also strong association of computed tomography findings with the progression of the disease, based on high resolution computed tomography[7]. Progressive patients had a higher prevalence of usual interstitial pneumonia pattern, reticulation, traction bronchiectasis, honeycombing and fibrotic extent >20%[8]. UIP pattern was still a significant predictor in the regression model[9]. These findings suggest that the presence of established fibrotic remodeling (on HRCT) is important for future progression[10]. The key finding of this study, however, was that there was also predictive value for extra-pulmonary signs, particularly digital ulcers, high skin score, mechanic's hands and peripheral neuropathy[11].

Progressive disease patients had higher inflammatory markers[12]. The progressive group had more often high ESR, CRP and creatine kinase[13]. An increase in CRP and ESR could be indicative of systemic inflammatory activity and an increase in creatine kinase could suggest inflammatory muscle involvement[14]. The results indicated that both inflammatory and fibrotic processes might be involved in CTD-ILD progression[15]. Monitoring of inflammatory markers may be helpful in supporting the clinical suspicion but should not be used as a substitute for pulmonary function tests and HRCT monitoring[16].

These findings of this study have significant clinical implications[1]. Re-epidemiological HRCT and advanced pulmonary function tests may not readily be available in many healthcare settings[2]. The examination of the skin and nervous system is simple, cheap and readily available[3]. The detection of digital ulcers, skin thickening, mechanic's hands and neuropathy at routine clinical examination may lead to the early identification of patients at high risk[4]. Consider frequent follow-up, early rheumatology-pulmonology collaboration, repeat pulmonary function testing and prompt treatment escalation in these patients[5].

The present study also indicates the need for a multidisciplinary approach to CTD-ILD[6]. Lung function and lung imaging studies tend to be the focus of pulmonologists, whereas rheumatologists detect systemic autoimmune activity[7]. Dermatologists can assist in describing the severity of the skin disease and do so; neurologists can confirm neuropathy, and/or myositis-related involvement[8]. These clinical aspects together could help to better stratify risk and identify patients with progressive fibrosing phenotype earlier[9].

There are some limitations in the study[10]. It was done in two centres of Multan with 100 patients which may be limited in generalisability[11]. Follow-up was relatively short and longer follow-up may detect other patients with delayed progression[12]. Some of the neurological presentations were made clinically, as nerve conduction studies were not performed in all patients[13]. Not all treatments were standardized, due to the dependence on the type, severity of disease and physician judgment for management[14]. With these limitations in mind, the study offers important clinical data suggesting that dermatologic and neurologic features may be useful to predict progressive fibrosing CTD-ILD[15].

Further investigations of larger multicenter cohorts with longer follow-up are suggested[16]. Prediction models could be improved by the incorporation of quantitative HRCT scoring, serial pulmonary function testing, nailfold capillaroscopy, nerve conduction studies, myositis-specific antibody panels, and serum biomarkers of fibrosis[1]. A practical risk score based on pulmonary, radiological, cutaneous, neurological and serological variables can be used as a tool to guide clinical monitoring and treatment in CTD-ILD[2].

CONCLUSION

A high prevalence of progressive fibrosing phenotype in patients with CTD-ILD was noted. There was a strong correlation between pulmonary progression and the presence of cutaneous and neurological manifestations. Digital ulcers, modified Rodnan skin score, mechanic's hands, peripheral neuropathy, UIP pattern on HRCT, and baseline FVC less than 70% predicted were independent predictors of progressive fibrosing phenotype. These findings indicate that thorough skin and neurological evaluation may be useful to obtain clinical data for early risk stratification of CTD-ILD patients. Closer pulmonary monitoring, multidisciplinary assessment and timely optimization of therapy should be considered in patients with these high risk features to minimize the risk of irreversible fibrotic progression.

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