Clinical Rheumatology (2021) 40:3455–3460
https://doi.org/10.1007/s10067-020-05336-5

BRIEF REPORT

Connective tissue disease-–associated interstitial lung disease: an underreported cause of interstitial lung disease in Sub-Saharan Africa

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Received: 9 July 2020 / Revised: 28 July 2020 / Accepted: 8 August 2020 / Published online: 15 August 2020

Abstract

Interstitial lung disease (ILD) occurs in 15% of connective tissue disease (CTD) patients causing considerable morbidity and mortality. Data is scarce regarding its clinical characteristics and outcomes in Africa. We aim to study the frequency, clinico-radiological characteristics, and treatment outcomes of African CTD-ILD patients. A retrospective cross-sectional study of ILD among 318 CTD patients diagnosed using relevant ACR criteria at the rheumatology unit of Lagos State University Teaching Hospital (LASUTH), Lagos from 2012 to 2019. Socio-demographics, clinical features, radiological findings, and treatment outcomes were documented. Data was analyzed using SPSS version 21 with $p < 0.05$. The LASUTH ethics committee approved the study. Interstitial lung disease occurred in 31 (9.7%) of 318 CTD cases. Their mean age was 38.8 ± 13.3 years, range 19–68 years with 28 (90.3%) females. Proportions of CTD-ILD were Sjogren's syndrome (50%), UCTD (50%), systemic sclerosis (46.7%), MCTD (33.3%), PM/DM (25%), SLE (6.5%), and RA (2.6%). Commonest presentations were cough (93.5%) and bibasal inspiratory crackles (83.9%) with a restrictive pattern in 83.9%. Antinuclear antibody occurred in 100% and anti-ENA in 67.7%. Traction bronchiectasis (89.7%) and ground glass opacities (96.6%) were frequent HRCT findings. Treatments included pulse-dose prednisolone, cyclophosphamide, mycophenolate mofetil, pirfenidone, and rituximab. Outcomes were ambulatory oxygen therapy (12.9%) and mortality (16.1%) with 9.7% lost to follow-up. CTD-ILD is a female predominant disease occurring in 9.7% of CTD patients mostly those with Sjogren's syndrome and systemic sclerosis. Due to significant morbidity and mortality, we advocate routine ILD screening for all CTD patients including those with undifferentiated disease.

Key Points:

- *Interstitial lung disease occurs in 9.7% of patients with underlying connective tissue*
- *Females are predominantly affected especially those with Sjogren's syndrome and systemic sclerosis.*
- *Mortality occurs in roughly 1 in every 6 patients with CTD-ILD.*

Keywords Connective tissue disease · Interstitial lung disease · Nigerians

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Introduction

Interstitial lung disease (ILD) is a diffuse parenchymal lung disease characterized by variable combinations of inflammation and fibrosis with shared clinical, radiological, and histological features [1]. The idiopathic type, represented by idiopathic pulmonary fibrosis (IPF), is the most common form with one-third representing those with identifiable causes such as environmental/occupational exposures, tobacco smoke, genetic susceptibility, drugs, radiation, infection, malignancy, and systemic autoimmune connective tissue diseases (CTDs) [2]. Connective tissue disease–associated interstitial lung diseases (CTD-ILD) are a subset that developed as a result of immune-mediated lung injury in patients with classifiable or undifferentiated CTD [3].

The specific etiology of CTD-ILD is not known but it is believed to be antibody and auto-reactive T cell–mediated attack on the lung tissues resulting in inflammation and fibrosis of the lung alveoli and interstitium [4]. Typically, CTD-ILD is a cause of considerable morbidity and mortality due to progressive decline in lung function sometimes leading to respiratory failure and death. Although CTD-ILD is associated with less mortality in comparison with idiopathic ILD, as a group, ILDs accounted for an 86% increase in years of life lost (YLLs) over a 13-year period [2]. The diagnosis often requires a combination of clinical, radiological, and sometimes histological features as patients can be asymptomatic. However, it can be daunting in patients without established or diagnosed CTD at the point of diagnosis of ILD.

The relative frequency of the CTD-ILD subtype is variable due to geographic and methodologic differences in addition to the heterogeneity of CTD. Nonetheless, it has been estimated to be around 15% among all CTDs [5]. In a recent review article, IPF and sarcoidosis were the most common causes of ILD in European countries with few reports from Asia, Latin America, and Africa [2]. In a study from Saudi-Arabia, CTD-ILD was documented as the most prevalent ILD [6]while African Americans were more likely to have CTD-ILD in comparison with Caucasians who were more likely to develop IPF [7].

Despite increasing African hospital–based reports of CTD and its severity as well as higher odds of diagnosis of CTD-ILD in patients of African descent living outside the continent, there is scanty data on CTD-ILD from Africa [7–9]. Interstitial lung disease was documented in 30% of Cameroonian CTD patients and 40% of systemic sclerosis patients in South Africa [10, 11]. Limited access to specialized medical and diagnostic services as well as poor health-seeking behavior in the region all contribute to under-recognition of CTD-ILD. We aimed to study the frequency, socio-demographics, clinico-radiologic findings, and treatment outcomes of CTD-ILD among patients in a tertiary hospital in Lagos, Nigeria.

Methodology

This was a cross-sectional study of ILD in CTD patients managed at the Rheumatology Unit of Lagos State University Teaching Hospital (LASUTH), Lagos, Nigeria. Some of the patients were referred from the respiratory unit after diagnosis of ILD was made with suspicion of CTD while others were diagnosed at rheumatology clinics or wards. We retrospectively collected data on all CTD-ILD cases diagnosed over a 7-year period (2012–2019). Rheumatoid arthritis, systemic sclerosis, systemic lupus erythematosus, Sjogren's syndrome, inflammatory myopathies, and mixed connective tissue disease were diagnosed according to relevant American College of Rheumatology criteria.

Clinical information including socio-demographics, signs and symptoms of ILD, pattern(s) of CTD, serology, pulmonary function, and radiology findings as well as treatment outcomes were retrieved from patients' records. The criterion for inclusion was having a diagnosis of CTD-ILD. Cases with a diagnosis of tuberculosis and other chronic primary pulmonary infections were excluded. Data was analyzed using statistical package for social sciences (SPSS) version 21 with a p value of < 0.05.

Ethical approval was granted by the Lagos State University Teaching Hospital ethics review board and the study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Results

Three hundred and forty-eight cases of CTD were diagnosed over the 7-year period out of which 30 cases had insufficient records. Three hundred and eighteen case files of CTD were finally retrieved for the study. These included systemic lupus erythematosus (n = 122), rheumatoid arthritis (n = 149), systemic sclerosis (n = 15), polymyositis/dermatomyositis (n = 12), primary Sjogren's syndrome (n = 6), mixed connective tissue disease (MCTD) (n = 6), and undifferentiated connective tissue disease (UCTD) (n = 8) as shown in Fig. 1.

There were 31 cases of CTD-ILD (9.7%) among 318 CTD cases. In decreasing proportion of occurrence compared with CTD frequency, Sjogren's syndrome (50%), UCTD (50%), systemic sclerosis (46.7%), MCTD (33.3%), PM/DM (25%), SLE (6.5%), and RA (2.6%) accounted for the 31 cases. Both conditions were diagnosed concurrently in 23 cases (74.2%) while chest clinic referrals accounted for the rest. The mean age of CTD-ILD patients was 38.8 (± 13.3) years with an age range from 19 to 68 years and 90.3% females. Cough (93.5%) and difficulty in breathing (71%) were the most common symptoms while bibasal inspiratory crackle was the most frequent sign (83.9%) as shown in Table 1. For serological tests,

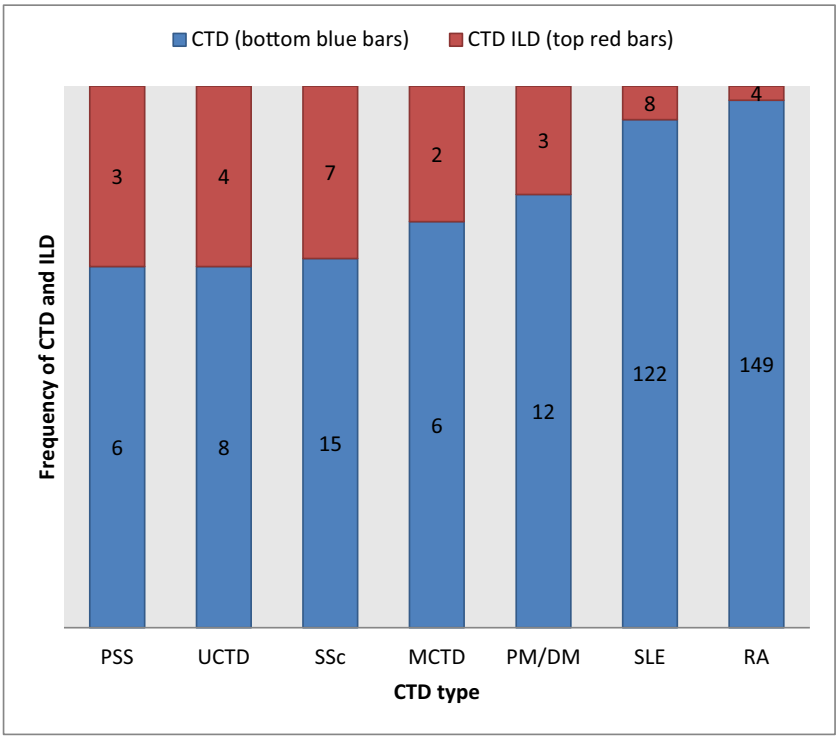

Fig. 1 Composite bar chart showing the occurrence of ILD in different CTDs

anti-nuclear antibody (ANA) was positive in all cases while extractable nuclear antigens (ENA) occurred in about two-thirds (67.8%).

Table 1 Socio-demographic and clinical characteristics of 31 CTD-ILD patients

Variables	*N* (%)
Age [mean (SD)] years	38.8 (± 13.3)
Age range (min-max) years	19–68
Duration of presenting complaint (median {IQR}) months	24 (10–60)
ILD diagnosed after diagnosis of CTD	8 (25.8)
ILD diagnosed same time with CTD	23 (74.2)
Female	28 (90.3)
Young age	20 (64.5)
Unemployed	11 (35.5)
Outdoor occupation	2 (6.5)
Marital status	15 (48.5)
Tobacco smoking	0 (0)
Cough	29 (93.5)
Dyspnea	22 (71)
Chest pain	10 (32.3)
Fatigue	17 (54.8)
Central cyanosis	17 (54.8)
Digital clubbing	7 (22.8)
Bibasal inspiratory crackles	26 (83.9)
Loud P2	7 (22.8)
Third heart sound	5 (18.1)

Traction bronchiectasis and ground glass opacities were the most prevalent high-resolution CT (HRCT) abnormalities seen in 96.6% and 89.7%, respectively. A mixed pattern of non-specific interstitial pneumonia (NSIP)/usual interstitial pneumonia (UIP) was the most predominant HRCT-based pattern (51.7%) and restrictive lung function observed in 26 cases (83.9%) as shown in Table 2. Figure 2 is a HRCT image of one of our patients showing diffuse ground glass and reticular opacities.

Cyclophosphamide ($n = 17$, 54.8%) and mycophenolate mofetil ($n = 10$, 32.2%) were the predominant immunosuppressants given in our series following initial pulse prednisolone in all patients. A quarter of the cases (25.8%) received phosphodiesterase V inhibitors (sildenafil/tadalafil) while rituximab and pirfenidone were given to 3 (9.7%) and 2 (6.2%) patients, respectively. Five patients died (16.1%), and 21 patients (67.7%) were still on treatment while the remainder (16.1%) were lost to follow-up. The cause of death was a respiratory failure in 3 patients, 1 had a cardiac arrest from acid-base disorder, and another 1 had superimposed severe pneumonia.

Discussion

The frequency of CTD-ILD of 9.7% in our study is lower than the frequency of 30% documented among 54 Cameroonians with CTD and fairly close to the estimated frequency of 15% reported in the literature [5, 10]. While some studies determined the prevalence in relation to all cases of ILD [2, 6, 7,

Table 2 Serology, pulmonary function, and imaging characteristics of 31 CTD-ILD cases

Variables	*N* (%)
ANA	31 (100)
Pattern—fine speckled	19 (61.3)
ENA	21 (67.8)
Anti-dsDNA	10 (32.2)
Anti-U1-RNP	2 (6.5)
Anti-Ro/SSA	3 (9.7)
Anti-La/SSB	2 (6.5)
Anti-Jo-1	2 (6.5)
Anti-MI-2	1 (3.2)
Rheumatoid factor RF	7 (22.6)
Anti-CCP	4 (12.9)
Anti-centromere	3 (9.7)
Anti-scl-70	5 (16.1)
Anti-RNA polymerase III	2 (6.5)
Echocardiography and PFT abnormalities	
Restrictive pattern	26 (83.9)
%FVC, mean (SD)	62.3 (14.2)
Desaturation at rest (SpO2 < 90%)	17 (54.8)
Pulmonary hypertension (N=25)	8 (32)
Right ventricular dysfunction (N=25)	5 (20)
HRCT abnormalities (N=29)	
Ground glass appearance	26 (89.7)
Reticular shadows	22 (75.9)
Traction bronchiectasis	28 (96.6)
Honeycombing	18 (62.1)
Reticulonodular opacities	7 (24.1)
Pleural effusion	4 (13.8)
Septal bullae	1 (3.4)
Diffuse alveolar opacities	1 (3.4)
Histologic correlates of HRCT findings	
1. NSIP pattern	10 (34.5)
2. NSIP/UIP mixed pattern	19 (51.7)
3. UIP pattern	4 (13.8)

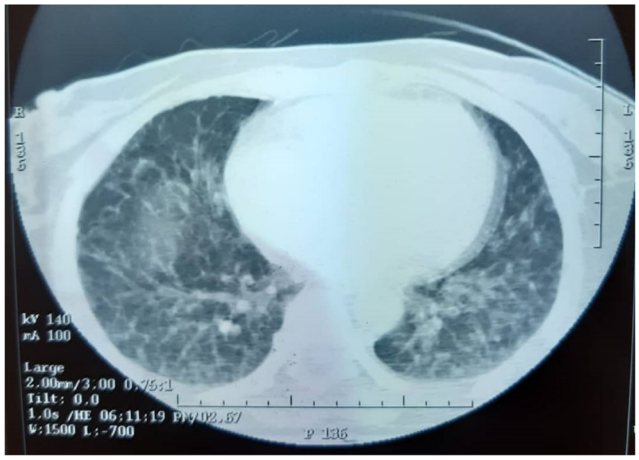

Fig. 2 HRCT image of a scleroderma patient showing ground glass and reticular opacities

9, 12], others calculated the prevalence in relation to all CTD, hence, the variability in prevalence reports [3–5, 10, 11, 13, 14]. In our practice, we usually request for a chest radiograph for all patients followed by a high-resolution CT scan though some patients cannot afford the latter due to financial constraints and lack of medical insurance. This scenario can result in the exclusion of subclinical radiographic ILD from our subjects which has been shown to be more prevalent than clinical ILD [14, 15].

Socio-demographic variables such as male sex, tobacco smoking, and older age have been identified as determinants of pulmonary function decline in CTD-ILD [16]. However, our patients were predominantly young females and non-smokers who were mostly engaged in indoor occupations [16]. Similar to a report by Doualla et al. in Yaoundé [10], cough and dyspnea were the most common symptoms while bibasal inspiratory crackles was the most documented respiratory sign. We also observed that most of our patients were diagnosed at the point of diagnosis of CTD. As CTD diagnosis is often delayed in Africa due to limited access to rheumatology and diagnostic services [8], it is not unexpected that the diagnosis of ILD in CTD may also be delayed with potentially higher morbidity and mortality.

Certain CTDs have a higher occurrence of ILD such as systemic sclerosis, inflammatory myopathies, and rheumatoid arthritis especially in developing countries [2]. From our study, ILD occurred in 46.7% of patients with systemic sclerosis similar to the 40% recorded from South Africa by Ashmore et al. [11] Interstitial lung disease also commonly occurs in patients with undifferentiated connective tissue disease with a figure of 44.1% documented from India [12] among patients with CTD-ILD comparable with the 50% occurrence in our patients. Despite its systemic nature, lupus has a relatively low occurrence of ILD as noted in our cohort and others [2, 12].

Undifferentiated CTD-ILD included patients with ILD at presentation who did not fulfill the criteria for a specific CTD. This entity has been designated Interstitial Pneumonia with Autoimmune Features (IPAF) by the European Respiratory Society (ERS)/American Thoracic Society (ATS) Task Force on Undifferentiated Forms of Connective Tissue Disease-associated ILD [17]. It is estimated that up to 25% of patients with features of CTD do not meet the criteria for a specific and defined CTD entity [13]. On the other hand, 10 to 20% of patients with idiopathic interstitial pneumonia have some clinical and laboratory features of a defined CTD [13]. The IPAF entity is emerging as a leading cause of CTD-ILD and is easily missed in resource-poor settings where presumptive disease classification based on limited investigations are common.

The serologic findings observed in this study reflect the pattern for background CTD. In tandem with previous reports [13, 14], antinuclear antibody was the most common antibody observed with majority having fine speckled patterns. The importance of ANA has recently come to the limelight in the recent IPAF classification criteria which proposed either ANA of 1:320 titer with a diffuse, speckled, homogeneous pattern or ANA of any titer with nucleolar/centromere pattern as one of the serological domains needed to classify a patient as having IPAF [14, 17].

High-resolution CT is the imaging modality of choice for detecting the presence, pattern, and severity of ILD in CTD as shown in Fig. 2 [3, 18]. The imaging pattern and extent of ILD seen on HRCT have been shown to correlate with histopathologic patterns and degree of pulmonary functional impairment [3, 19]. All idiopathic interstitial pneumonia (IIP) histopathologic patterns seen on lung biopsy can be seen in CTD-ILD though lung biopsy is only indicated in patients with CTD-ILD and atypical radiographic findings or clinical features that question the diagnosis [20].

There are currently no accepted guidelines or approved drugs for CTD-ILD in general. This is probably due to the heterogeneity of the pulmonary disease in various forms of CTD with a consequent paucity of high quality evidence upon which guidelines may be developed [15, 21]. However, the management of SSc-ILD has led the way in the amount of evidence available to guide the physician. Experts often extrapolate from the management recommendation for SSs-ILD to treat ILD in other CTDs [21–25].

In comparison with idiopathic ILD, CTD-ILD is generally associated with a better prognosis and it is more likely to respond to treatment with immunosuppressives. However, patients with CTD-ILD, when compared with those with CTD alone, face a worse prognosis [3, 21]. Recently, it was shown that African-Americans with CTD-ILD have significant survival benefit which has been attributed to shared genetic variants, differential autoantibody profiles, and low prevalence of fibrosis at presentation [7]. Unfortunately, our patients still face a grim outlook in Africa where quality healthcare is beyond the reach of many [8].

The retrospective nature of this study is a limitation due to the problem of incomplete data. We also studied a small size with uncertainty about the time of onset of ILD in our CTD patients. Nonetheless, this study shows that ILD does occur among our CTD patients with ILD onset coinciding with or occurring after the diagnosis of CTD. We hope that this study will be followed by larger longitudinal multi-center studies in the near future.

Conclusion

Nigerian patients with ILD endure a potentially dismal fate occasioned by late presentation, delayed diagnosis, and a limited availability of quality specialized investigations and care. These patients exhibit a wide spectrum of radiographic patterns among which a mixed NSIP/UIP type is particularly common.

CTD-ILD is a female predominant disease occurring in 9.7% of Nigerian CTD patients mostly those with Sjogren's syndrome and systemic sclerosis. Due to significant morbidity and mortality, we advocate routine ILD screening for all CTD patients including those with undifferentiated disease.

Authors' contributions All authors contributed to the study conception and design. Material preparation, data collection, and analysis were done by Hakeem Olaosebikan, Richard Akintayo, and Ajibade Adenitan. The first draft was written by Hakeem Olaosebikan, Richard Akintayo, Olufunke Adeyeye, and Akpabio Akpabio and all authors commented on previous versions of the manuscript. All authors read and approved the final version.

Data availability Available on request.

Compliance with ethical standards

Ethical approval was granted by the Lagos State University Teaching Hospital ethics review board and the study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Disclosures None.

Ethics approval Ethics approval was granted.

Consent to participate Informed consent was obtained

Consent for publication All authors agreed to the final publication.

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