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ORIGINAL RESEARCH ARTICLE

Clinical, serological and radiological findings in patients with rheumatoid arthritis from Zanzibar comparing those with and without interstitial lung disease

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ABSTRACT

Objectives: To describe the prevalence, characteristics, and outcomes of patients with rheumatoid arthritis (RA) associated interstitial lung disease (ILD) in a multi-centre cohort. **Methods:** We collected data from 132 patients with RA prospectively over a four-year period. Baseline socio-demographic characteristics (age, sex, smoking status, disease duration, time to diagnosis) were obtained. Patients were also assessed clinically to determine articular disease activity as well as to identify any respiratory involvement. Baseline chest radiographs were requested for all participants and those with findings suggestive of possible lung disease underwent high-resolution computed tomography (HRCT) to assess whether ILD was present. All patients with confirmed ILD were given rituximab monotherapy at recommended doses. **Results:** From a cohort of 132 adult RA patients, four were found to have RA-ILD on HRCT giving a prevalence of 3%. They had a mean age of 55 ± 18.5 years with three of them being female. They had long standing RA with significant delay in time to diagnosis. None of our patients were smokers but all were strongly seropositive. Non-specific interstitial pneumonia (NSIP) was diagnosed in two patients while usual interstitial pneumonia (UIP) was diagnosed in the remaining two. All patients benefitted from rituximab monotherapy as evidenced by improvement in respiratory symptoms, combined with non-progression on repeat HRCT, in tandem with clinical disease activity scores. **Conclusion:** Although our patient numbers were small, our paper describes epidemiological differences in RA-ILD for our patients when compared with patients in the West. Rituximab showed promising results in our patients, but results must clearly be interpreted with caution.

Keywords: rheumatoid arthritis; interstitial lung disease; usual interstitial pneumonia; non-specific interstitial pneumonia

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1. Introduction

The prevalence of interstitial lung disease (ILD) in patients with rheumatoid arthritis (RA) varies widely. Worldwide, high resolution computed tomography (HRCT) studies offer estimates as high as 40%[1] while clinical estimates are much lower, ranging from 1%[2] to 15%[3]. Most of these estimates come from Europe and America[3,4]. Studies from sub-Saharan Africa are sparse. A study from South Africa found a prevalence of RA-ILD of almost 30% using both pulmonary function tests (PFTs) and HRCT but most patients were of Indian origin[5]. By contrast, in Nigeria, a review of 318 patients with connective tissue disease reported a prevalence of 2.6% among those with RA[6]. A recent review of RA in Africa did not even list ILD among the systemic features it described[7].

Lung disease can predate the onset of articular involvement[8,9] and may be subclinical in older patients[2]. It contributes significantly to both morbidity and mortality among RA patients[10] and the most common form of ILD is usual interstitial pneumonia (UIP) which carries the worst prognosis[11]. Risk factors for ILD include older age, male sex, smoking, active articular disease and seropositivity to rheumatoid factor (RF) and cyclic citrullinated peptide (CCP)[12,13]. Shared genetic risk factors between the RA-ILD phenotype and familial pulmonary fibrosis were reported in 2017[14]. A year later the MUC5B promoter variant was reported as a predictor for RA-ILD in European patients but is reportedly rare in Asian and African populations[15]. Current recommendations such as the European Alliance of Associations for Rheumatology (EULAR) and the American College of Rheumatology (ACR) do not offer specific recommendations for the management of RA-ILD. They do however recommend a multidisciplinary approach[16]. Treatment options have recently been summarized[17,18], and initial reports of a favourable response to rituximab[19] have been supported by a large registry study which confirmed that this agent is effective in reducing or halting progression of ILD in many RA patients[20]. Work has now commenced on the development of an evidence-base to guide future therapeutic intervention via the British Society of Rheumatology and the British Thoracic Society.

Patients with RA-ILD may present with pulmonary symptoms such as dry cough or breathlessness, and symptoms may predate articular involvement. On physical examination, bi-basal respiratory crackles which fail to clear on coughing are usually audible. Chest radiography is insensitive, while PFTs are non-specific. The gold standard test for diagnosis of ILD is now HRCT which can define both the subtype and extent of disease[21]. Newer techniques such as lung ultrasound are being explored[22].

This study aims to describe the patient characteristics, prevalence, and forms of ILD from a cohort of RA patients in Zanzibar. To our knowledge this is the first such study reported from East Africa.

2. Materials and methods

Data was obtained from patients enrolled into a larger ongoing prospective cohort study on chronic inflammatory joint diseases (CIJD). All patients aged 18 years or over attending the rheumatology outpatient clinic at Mnazi Mmoja Hospital with a diagnosis of rheumatoid arthritis (RA) were invited to participate in the study. Mnazi Mmoja Hospital is a government referral hospital based on Unguja island. Additionally, patients meeting the inclusion criteria and attending outpatient clinics at two private hospitals based on Unguja island were also invited to participate. Only those who provided written and informed consent were recruited.

Socio-demographic data (age, gender, educational status, marital status, disease duration, time to diagnosis, smoking history, family history of rheumatological conditions and presence of other comorbid conditions) were collected. A full drug history, including all disease modifying anti-rheumatic drugs (DMARDs), was obtained. The history included functional limitations and the reason(s) for them. Respiratory symptoms were sought and recorded in all patients. Physical examination recorded all tender and swollen joints, deformities, and other relevant findings on physical examination, including chest crackles and finger clubbing. Data on relevant laboratory and radiological findings were also collected. All RA patients had a chest radiograph at baseline and if this was reported to be suggestive of lung disease, in the context of respiratory symptoms, then HRCT was arranged. The diagnosis of ILD was confirmed by HRCT, but pulmonary function tests (PFTs) and lung biopsy were not available.

Serological tests were undertaken but were confined to either rheumatoid factor (RF) or anti-cyclic citrullinated peptide (CCP). Anti-CCP was ordered only when RF was negative. Patients were placed on pre-specified treatment algorithms in line with international guidelines and had regular clinic visits following the treat-to-target (T2T) strategy. Those confirmed to have RA ILD on HRCT were commenced on rituximab therapy at the dose of 1gm intravenously on two occasions two weeks apart after confirming they had no

clinical or radiological evidence of tuberculosis. Descriptive statistics were used for presentation of the patient characteristics.

3. Results

3.1. Clinical and serological findings

At the time of this analysis, a total of 132 patients with RA had been recruited. The mean age of the cohort was 44 ± 13 years with 87% being female. The baseline clinical disease activity index (CDAI) at presentation indicated moderate disease activity. From our cohort, four participants were confirmed as having ILD on HRCT, giving a prevalence of ILD among our RA patients of 3%. **Table 1** shows the main demographic features. The mean age was 55 ± 18.5 years and of these patients three were female. All patients had articular features at the time of diagnosis with a significant median (SD) time delay of 3.5 years. None of the patients were smokers. Diagnosis of ILD was made at first assessment in two patients and during follow-up in two others.

Table 1. Demographics of four Zanzibari RA ILD patients at baseline.

Characteristic		**Patients with ILD**	**Patients without ILD**
Gender	(female)	3 (75%)	111 (87%)
Age	(mean, ± SD)	55 (± 18.5)	44 (± 12.9)
Disease duration* in years	(median, IQR	3.5 (2.5–12)	4 (2–6)
Time to diagnosis** in years	(median, IQR)	1 (0.5–10.5)	2 (1–4)
Disease activity based on CDAI scores	Baseline (median, IQR)	14.45 (9.3–21.5)	16.25 (8.7–25.75)
Serological status	Rheumatoid factor (RF) positive	2 (50%)	48 (58%)
	Anti-citrullinated protein (CCP) positive	2 (50%)	9 (11%)
Smoking history	Never	4 (100%)	117 (91%)
	Previous	0	8 (6%)
	Current	0	3 (2%)
Time of ILD diagnosis	At presentation	2 (50%)	NA
	At follow up	2 (50%)	
Symptoms	Dry cough	4 (100%)	NA
	Breathlessness	2 (50%)	

* Disease duration indicates total length of time from onset of symptoms to recruitment;
** Time to diagnosis indicates time from first symptoms to time diagnosis of rheumatoid arthritis is made;
CDAI—Clinical Disease Activity Index indicates high disease activity;
NA—Not applicable.

All the patients presented with dry cough and two reported exertional breathlessness. All patients had fine crackles on auscultation that failed to clear on coughing, and none presented with finger clubbing. High levels of RF were reported in two patients, and high anti-CCP concentrations in two others (7200 and > 340 Eu/ml (normal range 0–7) at baseline). All the patients presented with dry cough and two reported exertional breathlessness. All patients had fine crackles on auscultation.

3.2. Radiological findings

The HRCT scans findings were obtained from patient records and were generated after discussion among two or more radiologists (**Table 2**).

Table 2. Radiological findings from high resolution CT scan of the chest.

Patient description	High-resolution CT scan findings
Male, 70 years	Bilateral lower lobe pleural thickening, honeycombing, ground glass haze and cystic traction changes with traction bronchiectasis. Features were those of non-specific interstitial pneumonia (NSIP).
Female, 63 years	Bronchial tree dilatation with cylindrical bronchiectasis. Para-septal emphysema on both upper left and right lower lung lobes. Reticular opacities and traction bronchiectasis in basal segments of both lower lung zones. Features of fibrotic NSIP.
Female, 58 years	Predominantly right sided diffuse interlacing opacities, predominantly bi-basal associated with innumerable sub-pleural micro-cystic lesions obscuring the hemi-diaphragms with honeycombing consistent with usual interstitial pneumonia (UIP).
Female, 28 years*	Diffuse sub-pleural reticular opacities predominantly bi-basal more on the right side than left with cystic lesions and honeycombing. Features in keeping with UIP.

*Age at RA diagnosis was 27 years with 2-year duration from time of symptoms onset to time of diagnosis, clinical joint destruction, and overall poor adherence to medication.
CT—Computed Tomography.

At follow up, the participants with RA-ILD showed a positive response to rituximab therapy. All patients reported improvement in respiratory symptoms, one patient had a follow up HRCT scan which showed non-progression. All patients had improvement in their disease activity scores with a mean CDAI of 3.9 ± 3.5 indicating low disease activity.

4. Discussion

In the west, ILD has become one of the commonest co-morbidities seen in RA over the last 50 years[4,23,24] and it is strongly associated with increased mortality[25–27]. We were unable to find any previous data from East Africa on the prevalence of ILD in RA, and data from South Africa and Nigeria appear conflicting[5,6]. Our study suggests that ILD does occur in Zanzibari patients with RA and that the prevalence of clinically relevant ILD in RA patients may be in the region of 3%, in keeping with results from Nigeria. However, our patient numbers were small, and ascertainment may have been incomplete, as we only undertook HRCT in patients who had symptoms of ILD and an abnormality on their chest radiograph. Given the insensitivity of the latter in early ILD, it is very possible that we may have missed cases of early RA-ILD.

Although RA is a disease that predominantly affects women, literature from the West suggests that RA-ILD is typically a manifestation among older male smokers[13]. The data from the present study contrasts with some of these observations. None of the patients, including the only male, had any history of tobacco exposure. Indeed, smoking is rare in Zanzibar. However, the population is genetically distinct from that seen in mainland Africa, having some Arab, Indian and Persian ancestry. This genetic variance may explain some of the variance. A further potential factor relates to vitamin D exposure[28,29]. Most females in Zanzibar wear extensive clothing for religious reasons which markedly reduces their exposure to sunlight and may lead to a reduction in levels of vitamin D[30]. This may play a part in the immune response to antigens and the subsequent clinical expression of disease at an organ-specific level[31].

Table 3 compares and contrasts associations and features of RA-ILD between East Africa and the global West. There is a well-established link between high titres of both RF and anti-CCP levels and the development of ILD in RA[32], and this association is known to extend to populations worldwide[33]. All our patients with RA-ILD were strongly seropositive, in keeping with previous observations. The MUC5B gene has also been strongly associated with the development of RA-ILD[15,34]. However, this gene has not been studied in RA populations in sub-Saharan Africa (SSA) but from studies done in the West, it is reported to be less prevalent in persons of African ancestry[35]. Biomarkers are thought likely to be valuable in the prediction of future outcomes of RA and ILD[36,37], but, as yet this is unexplored territory within SSA populations.

Table 3. Patterns of RA-ILD in East Africa compared to the West.

	East Africa	West*
Clinical prevalence	2%–5%[6]	4%–10%
Age	Younger age	Older age
Smoking history	Non-smokers	Smokers
Disease duration	Long disease duration	Long disease duration
Disease severity	Severe disease	Severe disease
MUC5B gene	Rarely identified[33]	Strong association

* West defined as Europe and North America[1–4].

Currently, there are no international guidelines on the treatment of RA-ILD. Methotrexate use has been associated with pneumonitis. Recent data however suggests that methotrexate may not increase the risk of developing ILD in RA, and that it may be protective in this regard[38,39]. By contrast, evidence has accumulated to suggest that anti-TNF therapy might be associated with worsening outcomes in RA-ILD[39] but evidence is inconclusive. Other biological agents are however, often preferred over anti-TNF agents as treatment for active articular RA in the presence of established ILD[39]. Rituximab has been shown to be an effective option for both the articular manifestations of RA and for comorbid ILD[18–20,40]. In our study all patients were commenced on rituximab monotherapy and showed improvement in their respiratory and their articular symptoms. Where HRCT was repeated, this confirmed stability. We did not use concomitant methotrexate in our patients for cost purposes. This is always an important consideration in SSA, as patients often must pay for their therapy and many struggle to afford it. In Zanzibar, rituximab is available free of charge while oral disease modifying therapies are relatively expensive when not available at the hospital pharmacy. When allied to the fact that many of the therapeutic agents available in the west are simply not available in SSA, this limits the number of therapeutic options for the treatment of RA-ILD quite severely. Agents which have proven efficacy in RA-ILD, such as abatacept[41,42] and the anti-fibrotic drugs[43], are inaccessible at present across Zanzibar and most of East Africa. However, there is some evidence that the orally administered JAK inhibitors may prove effective in the treatment of RA-ILD[44,45], and these drugs are becoming available in SSA, and at a price that is significantly cheaper than the cost of using triple DMARD therapy for active RA. Given that large numbers of people in SSA have limited access to both electricity and transport, affordable orally administered agents which offer effective relief might prove a huge advantage over parenteral therapy in future.

5. Conclusion

This is the first paper to describe the prevalence and clinical features of ILD among RA patients in East Africa. We have identified potentially important epidemiological differences in the pattern of disease in Zanzibari patients compared to that reported in the West, although seropositivity and high articular disease activity remained associated with the development of ILD in this study. Although numbers are small, obliging caution with regards to our estimates of prevalence and therapeutic responsiveness, there is early encouragement that a good therapeutic response can be obtained with the limited therapeutic agents presently available.

Author contributions

Conceptualization, KC and SS; methodology, KC and SS; software, SS; validation, SS, ON and JF; formal analysis, SS; investigation, SS, ON and JF; resources, SS; data curation, SS; writing—original draft preparation, KC and SS; writing—review and editing, KC and SS; visualization, SS; supervision, KC; project administration, SS; funding acquisition, SS. All authors have read and agreed to the published version of the manuscript.

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Ethics

Ethical approval was sought from the Zanzibar Health Research Institute and granted under the approval number ZAHREC/02/JULY/2019/43.

Conflict of interest

The authors declare no conflict of interest.

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