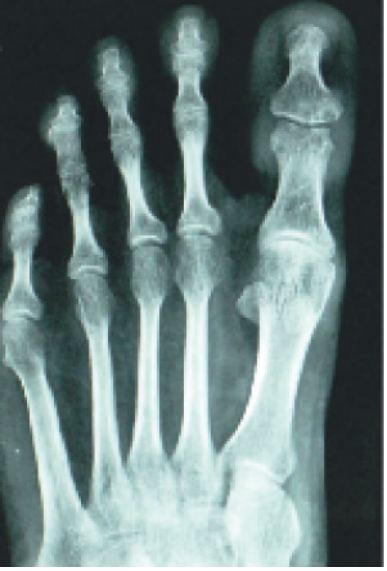

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Call for action: development of patient registries in Africa

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Rheumatology registries are essential tools for understanding the burden and impact of musculoskeletal and autoimmune diseases in Africa and improving the diagnosis, treatment, and management of these conditions. A call for action is needed to establish and maintain these registries on the continent. The need for rheumatology registries in Africa is urgent and requires immediate action. Rheumatology registries are databases that collect and store information about patients with rheumatologic conditions, such as rheumatoid arthritis, lupus, and osteoarthritis. These registries can provide valuable data on the epidemiology, burden, and outcomes of these conditions in the African population. However, currently, there are very few rheumatology registries in Africa, and there is a pressing need to establish more of them. Examples are a few, such as the Biologic registries in South Africa and Tunisia[1]. One primary reason for the need for African rheumatology registries is the lack of data on the continent's epidemiology and burden of musculoskeletal and autoimmune diseases. With accurate data, it is easier to understand these conditions' scope and impact and develop effective strategies for addressing them. Rheumatology registries can fill this gap by providing data on the incidence, prevalence, and outcomes of musculoskeletal and autoimmune diseases in different populations. This information can inform public health policies and guide the allocation of resources for research and care. The paucity of epidemiological data is partly driven by the low number of practicing rheumatologists in Africa[2]. Establishing more rheumatology registries in Africa, there is a call for action to the government, healthcare organizations, academic institutions, patient organizations, and the international community to invest in developing and maintaining these registries. This includes funding for the development of registries, training for healthcare professionals on how to use them, and resources for data management and analysis[1]. A survey conducted in the year 2020 revealed that about 150 rheumatologists are serving approximately 1 billion people in sub-Saharan Africa, which is below the ideal ratio of one specialist to 150,000 populace[3]. Secondly, registries can help to improve the diagnosis and treatment of these conditions by providing healthcare professionals with access to accurate and up-to-date information on patient demographics, disease characteristics, and treatment responses. The outcome will be more accurate diagnoses, better treatment decisions, and improved outcomes for patients. In addition, registries can also be used to monitor the safety and effectiveness of treatments, which can be crucial for ensuring that patients receive safe and effective care. Registries aid in identifying any potential side effects or adverse reactions to medicines, which will improve patient care and safety in the future.

An example is the SABIO registry that evaluated the rate of tuberculosis (TB), the effectiveness of the latent TB infection (LTBI) program, risk factors, and outcomes in South African patients using biologics for rheumatic diseases[4]. Furthermore, registries can monitor the quality of care for patients with musculoskeletal and autoimmune diseases. Data will help to identify areas where improvements are needed and to develop strategies to improve the overall quality of care. Another critical aspect of rheumatology registries is that they can provide valuable data for international comparisons and collaborations. Africa is a diverse continent with different cultures, languages, and health systems, and it is essential to understand each country's specific challenges and opportunities. Achieving these targets will require to accomplish a call for action to the government, healthcare organizations, and the international community to invest in developing and maintaining rheumatology registries in Africa. This includes funding for the creation of these registries, as well as resources for data collection and analysis.

Moreover, collaboration and partnerships between stakeholders, including academic institutions, healthcare providers, patient organizations, and the private sector, can play a crucial role in developing African rheumatology registries. Lastly, we can use the data collected in these registries to support research and the development of new treatment options. The data can help to improve the understanding of these conditions and to identify new targets for therapy better suited for the African continent.

In conclusion, the need for rheumatology registries in Africa is urgent. It is essential to invest in the development and maintenance of these registries to address the high burden of musculoskeletal and autoimmune diseases on the continent. A call for action is needed to establish and maintain these registries on the continent to improve the understanding of the epidemiology, improve the diagnosis and treatment, ensure safe and effective care, monitor the quality of care, and support research and new treatment options. Moreover, collaboration and partnerships between stakeholders, including academic institutions, healthcare providers, patient organizations, and the private sector, can play a crucial role in developing African rheumatology registries.

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Arthritis in East Africa: an observational study

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Abstract

Background: The burden of musculoskeletal (MSK) disease in East Africa remains largely unknown. Early evidence from Tanzania suggests that it may have a substantial adverse impact on health care outcomes, with both social and economic consequences. Limited data on prevalence and case mix of MSK disorders is presently available for East Africa. Data is urgently required to facilitate the planning, provision and funding of the services needed to meet population requirements here. The need is likely to be greatest among the poorer and most isolated members of the community.
Objective: This study describes the case mix of MSK disorders we encountered among people across five regions who had no previous access to clinical care in East Africa.
Methods: Over a four-week period in 2022, we undertook a series of clinics in five separate locations across impoverished areas of Zambia and Kenya. These ranged from city slums to isolated rural communities. We recorded demographic features for every consultation, along with our diagnosis and intervention. We calculated the percentage of people consulting with MSK issues and describe the case mix of MSK disorders, along with interventions provided.
Results: A total of 1089 community consultations in Zambia and Kenya were completed. Of these, a total of 271 people (24.9% were completed) reported primary MSK issues. This population was mainly female (66%) and had a median (range) age of 58 (13-90) years. The percentage of patients who consulted with MSK issues were significantly influenced by geographic location, rising from 8% in urban areas to 52% in the most rural sites. The commonest MSK diagnoses found at first consultation were osteoarthritis (49.8%), mechanical low back pain (27.7%) and soft tissue rheumatism (10.0%), with 3.0% having evidence of Inflammatory Joint Disease (IJD). Therapeutic intervention was provided in 62.3% and procedures were performed in 11.4%.
Conclusions: MSK disease appears to be a common reason for seeking medical intervention in East Africa, especially among older females who have accumulated a significant mechanical burden from physical exertion and childbearing. Therapeutic intervention was frequently required, although smaller numbers had evidence of IJD. Increased awareness of the burden of MSK disease on poorer populations is necessary. Training programs in rheumatology are urgently required to ensure that care pathways are established with adequate funding and regular rapid access to ensure the provision of appropriate support and intervention.

Key words: Rheumatology, Osteoarthritis, Zambia, Kenya, Musculoskeletal

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Introduction

It appears that modern humans evolved about 300,000 years ago via merging of populations across South and East Africa, and that the rift valley was their ancestral home. Despite this, our knowledge of the burden of musculoskeletal (MSK) disease in Sub-Saharan Africa (SSA) remains extremely limited. There has been little evidence of inflammatory arthritis detected in human skeletal remains from SSA until relatively recently[1]. Clinicians have now confirmed the presence of MSK disease in SSA and highlighted the need for more data[2]. The World Health Organisation has identified that SSA has the lowest ratio of doctors to population in the world and that this shortage extends to all categories of health-care personnel[3].

The Community Oriented Program for Control of Rheumatic Diseases (COPCORD) approach was proposed to improve data collection and standardisation in areas including SSA[4] and this approach has been adopted with success[5]. However, this suggested that most patients identified already exhibited advanced disease and deformity, and this was especially true of those living in rural or impoverished communities[5]. Although the opportunity to develop and improve

rheumatological services was highlighted in 2017[6,7], five years later there has been limited evidence of progress[8].

Given the limited data on prevalence and case mix of MSK disorders available within SSA, more data is urgently required to facilitate the planning, provision and funding of the services needed to meet population requirements for clinical care. The need is likely to be greatest among the poorer and most isolated members of the community. We describe the case mix of MSK disorders we encountered among people across five impoverished regions of SSA, very few of whom had any previous access to clinical care.

Materials and methods

This was an observational study based on our clinical experience during a four-week period in 2022, when we undertook a series of clinics in five separate locations across impoverished areas of Zambia and Kenya. These ranged from city slums in Lusaka and Nakuru to isolated rural communities in both countries. Very few of the attenders at our clinics had any prior access to medical care and no medical notes were available for any patient. Two of us worked together (LB and CK), while another worked independently (CAK). CAK also assessed all other cases where diagnostic or management issues arose. Most clinics were held in school classrooms except at one very remote location centred near Siavonga in southern Zambia where there were no public buildings. Here clinics were held outdoors under the shade of two large baobab trees.

Clinical assessment was based on history and examination. As different languages were spoken at each site, a local health care worker was employed at each clinic, and served as translator, chaperone and clinical assistant. The clinicians had equipment to measure blood pressure, blood sugar, arterial oxygen saturation and to perform urinalysis. However, very limited access to any form of other investigation existed with blood tests (haemoglobin, creatinine, Erythrocyte Sedimentation Rate (ESR) and Rheumatoid Factor (RF) only available at one site. Likewise, only a single site had any facilities for radiological investigation, and even there this was confined to plain joint and spinal radiographs. No facilities for microscopy were available at any of the clinic sites.

Demographic features including age and gender were recorded for every consultation, along with the diagnosis and all therapeutic interventions. We calculated the age and gender mix, along with the percentage of people consulting with MSK issues. We defined the case mix of MSK disorders, along with all investigations and interventions provided. Patients often reported that their joints were swollen, and this was corroborated by physical examination which often showed large effusions in warm tender joints. Where clinicians judged it to be necessary, joint aspiration with or without injection of intra-articular steroids, was performed using a 'no touch' approach using gloves and a sterile field. Fluid obtained from joint aspiration could not be analysed locally and was sent to the nearest hospital laboratory only if sepsis was suspected. MSK diagnoses were based on validated tools, but the absence of certain investigations reduced diagnostic precision and inevitably led to a few cases where no diagnosis could be made.

Funding for the clinics and the medication was provided by the relevant charity. This was 'Opportunities Zambia' for the three sites in Zambia, while the Catholic Diocese of Nakuru funded clinics at the two Kenyan sites. The expenses of the three clinicians were met entirely by themselves and they were not paid for their work. Patients were given a starter pack of medication where this was required and instructed on how to renew this if necessary. They were neither charged nor financially rewarded for attending clinics which were held on an open-ended basis without prebooked appointments. As such, clinics contained a wide range of patients in terms of both numbers and clinical case mix. All patients were informed that their clinical data and personal details were anonymised, and all gave informed consent to these data being used to produce a scientific article with the intention of improving access to healthcare resources for poor communities in East Africa.

Results

A total of 1089 community consultations were completed in Zambia and Kenya over a period of four weeks across five separate sites. Of these, a total of 271 (24.9%) people reported that their primary complaint was of musculoskeletal (MSK) origin. This group had the highest median (range) age of all categories of diagnosis at 58 (13-90) years, and 179 (66%) of these were females. The percentage of patients within each clinic area who consulted with MSK issues was significantly related to geographic location, rising from just 8% in a central urban area, to 52% in the most rural locations in both Zambia and Kenya (Table 1).

The commonest MSK diagnoses we made at first consultation are shown in Table 2. Osteoarthritis accounted for half of all cases, with the knee easily the commonest site. Generalised nodal osteoarthritis affecting the fingers and thumbs was also frequently observed, while by contrast we documented only a single case of osteoarthritis affecting the hip. Mechanical low back pain was commonly reported, accounting for a quarter of all MSK consultations, while mechanical neck pain was reported in under 3% of individuals. All these conditions were more often seen in females. Soft tissue rheumatism accounted for 10% of MSK consultations and chiefly comprised of shoulder capsulitis, carpal tunnel syndrome and tenosynovitis. Chronic widespread pain and tenderness, fulfilling ACR criteria for fibromyalgia[9], was recorded in 2.6% patients, most of whom were females. Only 8 (3%) patients met the objective criteria for an inflammatory joint disease, with 6 having RA[10], and one each having Ps A[11] and AS[12]. Apart from a single

Table 1: The percentage of patients presenting with musculoskeletal symptoms compared to their geographic location

Zambia	
Kabanana (city slum)	45 (8%)
Chomwe (sub-urban)	53 (18%)
Siavonga region (very isolated and accessible only by boat)	114 (52%)
Kenya	
St Anthony's clinic near Nakuru (sub-urban)	29 (26%)
Momoi farm at Mbogoini (very isolated and rural)	30 (50%)

Table 2: The number (percentage) of musculoskeletal conditions (MSK) diagnosed in 271 patients presenting with MSK symptoms. Percentages of patients identifying as female are shown in square brackets [%]

Degenerative spinal disease	75 (27.7%) [82%]
Generalised OA	73 (26.9%) [72%]
OA knees	62 (22.9%) [71%]
Soft tissue problems(Capsulitis, CTS, tenosynovitis)	27 (10.0%) [52%]
Inflammatory joint disease	8 (3.0%) [88%]
Fibromyalgia	7 (2.6%) [86%]
Gout	3 (1.1%) [0]
Reactive arthritis	2 (0.7 %) [0]
Infection	2 (0.7 %) [0]
Giant cell arteritis	1 (0.4%) [100%]
No diagnosis made	11 (4.1%)

OA=Osteo Arthritis
CTS=Carpal Tunnel Syndrome

Table 3: A list of treatments administered to 211/271 patients

Non-steroid anti-inflammatory drugs	125 (46.1%)
Joint aspiration with steroid injection	25 (9.2%)
Joint aspiration without steroid injection	6 (2.2%)
Oral steroids	6 (2.2%)
Hydroxychloroquine	4 (1.5%)
Antibiotics	3 (1.1%)
Analgesia	42 (15.6%)

patient reporting a prior diagnosis of RA, these were all new diagnoses made by us in clinic and were based on history, examination and a limited range of investigations. Two patients gave a classic history of a reactive arthritis following recent documented infection. Radiology was arranged in 5 patients, while inflammatory markers were measured in 4 and serology was ordered in 2 patients. We used the results of all investigations to facilitate diagnoses for these patients, but we fully acknowledge that the scarcity of these tests meant that a secure diagnosis of some conditions was much more difficult to achieve. This severely limited any estimates of the frequency with which inflammatory joint disease occurred in this population.

Just three (1%) patients had clear clinical evidence of gout with tophi. This could well represent an underestimate as we were not able to access polarising light microscopy to examine synovial fluid for uric acid crystals. For similar reasons, the diagnosis of pyrophosphate arthropathy could not be made with any certainty. Given the large number of patients with sizeable knee joint effusions which we often aspirated, we might easily have misdiagnosed

crystal arthropathy as inflammatory osteoarthritis in a significant number of cases. Soft tissue rheumatism was also diagnosed exclusively on clinical grounds. Carpal Tunnel Syndrome (CTS) was diagnosed on the basis of appropriate symptoms associated with thenar wasting, sensory discrimination and a positive circle test.

Two further patients had septic arthritis and required us to arrange urgent hospital admission for drainage and intravenous antibiotics. One other patient required oral antibiotics for an infected bursitis. One patient had classic giant cell arteritis with grossly elevated ESR. We were unable to make a confident diagnosis in a total of 11 (4%) patients.

Table 3 documents the therapeutic intervention offered to all patients presenting with features of MSK disorders. Non-steroidal Anti-inflammatory Drugs (NSAIDs) were provided to around half of all patients, with paracetamol given to a further 15%. In 31 (11%) patients with clinical evidence of a joint effusion, we aspirated synovial fluid for therapeutic purposes. Twenty five of these were given an Intra-Articular Steroid (IAS) injection for symptomatic relief. The knee was the commonest site requiring a procedure, with two patients needing IAS to the wrist and one each to the shoulder and ankle. For patients with IJD, oral steroids were often provided for a short period. Those with RA were offered hydroxychloroquine which was accepted by four patients. The single patient with GCA was given high dose steroids and an urgent review was requested at the nearest hospital.

Discussion

This study shows that MSK disease accounted for a quarter of all community consultations among those residing in poverty in East Africa. By comparison with those who consulted for other indications, people with MSK concerns were more likely to be older, female and residing in a rural location with little access to any medical care. Females are often responsible for much of the manual work in rural Africa, frequently expected to plant and harvest food crops, as well as prepare the food for their family. This is in addition to their role as mothers which they often conduct in tandem with manual labour, carrying their younger children on their backs. It is no surprise that they often accumulate a significant mechanical burden from the combination of physical exertion and childbearing. Such demands often commence at a young age and remain common practice in rural East Africa where motorised vehicles and mechanical aids are a rarity.

Some data on the case mix of MSK disorders has been made available from inpatient and outpatient hospital settings in SSA[13,14], but these are scanty and heavily influenced by accessibility and affordability. Hence, they can provide neither reliable estimates of disease prevalence, nor data on the distribution of rheumatological disease in the community.

However, a large systematic review and meta-analysis reviewing 27 studies over the forty years prior to 2015 did identify a range of MSK disorders across Africa[15]. Although twelve of the studies came from South Africa, the results revealed a significant prevalence of each of osteoarthritis (OA), Rheumatoid Arthritis (RA), and gout. Psoriatic Arthritis (PsA) was identified in urban South Africa, while Juvenile Inflammatory Arthritis (JIA) and Ankylosing Spondylitis (AS) appeared to be relatively rare throughout Africa[15].

Recent evidence from Tanzania suggests that MSK disease may have a substantial impact on health care outcomes, with both adverse social and economic consequences[16]. However, even now detailed information on the prevalence and case mix of these disorders is largely lacking in East Africa. From the limited data available, it seems likely that OA is the most prevalent MSK disorder across communities in SSA, with prevalence estimates ranging from 30% up to 83%. Rural location and increasing age appeared to be associated with the highest prevalence[15] but the threshold for diagnosis was low in several of the quoted studies. The knee appears to be the commonest site of OA with a prevalence of 33.1% reported among rural communities in South Africa. Equivalent data from other countries in SSA is scanty at present but an observational study in a hospital setting reinforced the impression that the knee is the commonest site with clinical evidence of this condition[17].

This study found that osteoarthritis of the knees was the commonest presentation of articular disease and was associated with considerable impairment of function. Although we did not formally quantify this, many people described being unable to work, or even to walk, as the result of pain and associated swelling. In the absence of investigations such as X-ray and polarising light microscopy, the presence of a secondary crystal arthropathy could not be excluded or confirmed. However, affected joints frequently yielded 50 millilitres of viscous synovial fluid when aspirated and patients reported dramatic benefit from the introduction of an intra-articular steroid preparation, as evidenced by later feedback to the local study coordinators. People who had no knee effusions were treated with NSAIDs. Previous work has confirmed those of African heritage are more prone to degenerative disease in the knees[18-20] and suggested that this might be influenced by genetic factors. By contrast, we saw only one case with clinical features to suggest osteoarthritis of the hips. The reasons for this observed difference are not entirely understood, but the structure and function of the hip joint in Africans may differ from Caucasians which could offer some protection from later degenerative disease. However, one study has suggested that African Americans are more prone to radiological evidence of cartilage loss in the superior hip[21] although this may not correlate with clinical signs, symptoms or disability.

The lumbar spine was another common source of symptoms among those who consulted us. Degenerative

disc disease was frequently associated with reduced movement and with features of nerve root irritation. Again, the absence of investigations made detailed assessment difficult but there was a striking difference between the number of cases of mechanical lumbar and cervical origin. Indeed, there were few complaints of neck pain among women despite the tendency to carry heavy objects on their heads from an early age. We theorise that the neck muscles compensated and added to the capacity for loading bearing in the cervical area, preserving good posture in the upper spine. By comparison, an exaggerated lumbar lordosis was usually observed in women with low back pain and may be an adaptation to carrying a succession of babies over a prolonged period. Radiological evidence again supports the finding of increased degenerative disease in the lumbar spine among African women[22]. Environmental factors therefore may be more relevant than genetic factors in determining the observed differences in the precise location of degenerative change in the spine and lower limbs.

Although systemic inflammatory MSK disorders are now increasingly recognised across Africa[23], a decade ago there was very little data on the prevalence of RA in the continent[24]. Indeed, there is good evidence that RA has only been recognised in Africa within the last 65 years[1]. The community prevalence of RA ranges widely from 0.1% to 2.5% in urban populations, with lower rates in rural areas. These data were largely derived from North and South Africa[15], with a higher prevalence in urban areas and among smokers. Late presentation remains typical and the prevalence of seropositivity appears lower than in western countries[25]. A pattern of later presentation of RA, delayed diagnosis and limited management options for African patients has emerged when compared to those countries with a more developed health care system[26-28].

The number of people in whom we were able to make a confident diagnosis of inflammatory joint disease was relatively low, although six people did meet criteria for RA. There is evidence that this condition is less common in rural Africa and is concentrated in urban areas[23-25]. In the absence of confirmatory investigations, this may be an under-estimate of the number of cases among those who consulted us, and our data cannot be used to assess the prevalence of any of the conditions we encountered. There are clearly many present challenges to the provision of modern rheumatological care in rural East Africa.

These include access to adequate training for local health care providers, limited access to and affordability of investigations and very limited therapeutic options. Relatively few African countries have a registry of the use of biologic agents in RA (South Africa, Egypt, Algeria and Morocco) and some still have no access to any biologic treatments.

Soft tissue MSK complaints accounted for 10% of all rheumatological consultations. Conditions like shoulder capsulitis and CTS usually respond well to low-cost interventions, but again require a degree of expertise and investment to provide this. Less amenable to a one-off intervention is chronic pain, and we did encounter a few cases, usually in the context of fibromyalgia. The complex interaction between physical and psychological factors involved is more difficult to address in rural East Africa than in the UK.

The prevalence of gout in SSA had been thought to be low until recently[29] but this disorder is now increasing within certain populations, as reported in Nigeria and Kenya, among others[25]. This is multi-factorial but associates with each of increasing obesity, urbanisation and alcohol consumption. It remains a marker for later vascular disease, especially among those with a polyarticular presentation which is not uncommon and affects the knees and ankles more often than the first metatarsophalangeal joint by contrast with the western experience[25]. Gout is more readily recognised in SSA as risk factors increase. Again, this is less of a feature in poorer rural areas where obesity and alcohol excess are less common. Increased awareness of this eminently treatable disorder amongst both the population and health care staff is warranted. By contrast, both psoriatic arthritis and ankylosing spondylitis were rare among the population attending our clinics, and this observation is supported by the published evidence from elsewhere in Africa[15].

Infection still plays a part in the morbidity associated with MSK disease, but we were surprised at the relative lack of serious infective complications affecting bones and joints among the population we saw. Direct articular infection was rare, while reactive arthritis was associated, as expected, with prior suspected streptococcal or sexually acquired infection.

Again, awareness of these complications is important, especially among a population where HIV infection, brucellosis and tuberculosis are all still quite prevalent in the community. By comparison, inflammatory joint disorders in children appear rare. A recent survey of MSK disorders among those under 18 years in Tanzania failed to reveal any cases, with most of the limited pathology relating to traumatic joint or bone disease with a subsequent high rate of local complications[30].

We worked alongside several local doctors and other health care workers in clinics to train them in the process of diagnosing and managing MSK disease and they were all enthusiastic and rapid learners. However, the management of IJD's and systemic connective tissue disorders require considerable experience and access to prescribing and monitoring services which are not always easily provided or afforded in the areas where we were working. A recent systematic review and meta-analysis of a large hospital population calculated a prevalence of Systemic Lupus Erythematosus (SLE) of 1.7%. Renal involvement was very high, affecting between one third and one half of patients[31]. Given that we found no cases of SLE, patients with this condition may present later than they do in other countries. The opportunity to intervene effectively at an earlier stage

would be enhanced by greater population awareness. A screening program to look for proteinuria and systolic hypertension among young women may yield dividends but requires more investment in public health. Expanding training and education for health care staff must be made a high priority in SSA.

There are several obvious limitations of our study, including the difficulty in accessing investigations to clarify and confirm clinical diagnoses. No conclusions about prevalence can be made from the observational data we collected. Several types of autoimmune disease could not be diagnosed with any confidence, under such circumstances. Thus, conclusions relating to SLE and other connective tissue disorders could not be drawn from our data.

Africa faces several medical challenges including underfunded public health and medical management, inefficient utilisation of resources, shortage of health care staff, and the lack of support for rural populations[32,33]. The gaps in care for NCDs are becoming increasingly well recognised[34].

Given that we have documented significant numbers of people with life limiting MSK disorders in East Africa, more investment in training and education is indicated for health care workers in this region. Whilst rheumatological services are now developed in Kenya and Tanzania, they remain almost exclusively city centric. Many rural dwellers are unaware of the need to seek help from medical staff and still opt to seek the services of the local witch doctor or try herbal remedies. This adds to the complications that accompany delayed diagnoses. As therapeutic intervention is frequently indicated, and usually effective, a significant expansion of services for MSK disease is indicated in East Africa and this must include improved access to investigations and to drug treatment. Such an approach should include recruitment and training of nurses, physiotherapists, and pharmacists into a wider multi-disciplinary team to provide more cohesive care for a population who may not be aware of the need or opportunity to seek medical help. Hence, management of these issues should also target patient populations at the systemic level as opposed to individualised treatment.

Conclusions

MSK disease appears to be a common reason for seeking medical intervention in East Africa, especially among older females who have accumulated a significant mechanical burden from physical exertion and childbearing. Therapeutic intervention is frequently required, and although we detected small numbers with IJD, the true prevalence of inflammatory and auto-immune disorders requires a more detailed approach. Increased awareness of the burden of MSK disease on poorer populations in Africa is necessary. Training programs in rheumatology are urgently required to ensure that care pathways are established with adequate funding and regular rapid access to ensure the provision of appropriate support and intervention.

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Adherence to disease modifying anti-rheumatic drugs among rheumatoid arthritis patients attending the Kenyatta National Hospital Rheumatology Clinic

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Abstract

Background: Rheumatoid Arthritis (RA) is a chronic multi-systemic disease characterised by inflammation of the synovial membranes of the joints. The cornerstone of treatment is with Disease Modifying Anti Rheumatic Drug (DMARD) therapy which includes synthetic and biologic agents. Adherence to RA treatment can be challenging as management requires a complex long-term interplay between the treating physician, medications used, the patient as well as their families and care-givers. Multiple factors contribute to variable adherence to therapy leading to treatment goals not being met. Assessing treatment adherence is therefore key to identifying and addressing the root causes of non-adherence.

Objective: To evaluate treatment adherence and clinical disease activity among rheumatoid arthritis patients attending the Kenyatta National Hospital Rheumatology Outpatient Clinic.

Methods: This was a descriptive cross-sectional study carried out at the Kenyatta National Hospital Rheumatology Outpatient Clinic. We recruited patients over the age of 18 years with a diagnosis of rheumatoid arthritis as diagnosed according to the 2010 ACR criteria on file and who had been on at least one DMARD for at least three months. The study tools that were used included a study proforma, the 5 item compliance questionnaire of rheumatology (CQR-5) to assess adherence and the Clinical Disease Activity Index (CDAI) to assess disease activity.

Results: A total of 97 patients, were recruited, 84.5% of whom were female and the mean age was 53.9 years. The overall level of adherence was 49.5% with a mean CQR-5 score (SD) of 15.8 (1.7). Moderate disease activity was noted in 85 (87.6%), patients 5 (5.2%) patients had low disease activity while 7 (7.2%) patients had high disease activity. No patient scored low enough to be categorized as being in remission. There was a significant association between age less than 62 years and adherence to DMARD therapy (p=0.032).

Conclusion: The level of adherence to DMARD therapy was lower than global averages and WHO recommendations. Most patients had moderate to high disease activity while no patients were found to be in remission. There was no statistically significant association between adherence to medication and disease activity.

Key words: Rheumatoid Arthritis, Adherence, Disease activity, Nairobi, CQR-5

Introduction

Rheumatoid Arthritis (RA) is a chronic systemic inflammatory disease of unknown aetiology. While it has several manifestations, it has a predilection for the joints wherein it causes a symmetrical polyarthritis which may initially be monoarticular. It is the commonest cause of chronic inflammatory arthritis and has an estimated worldwide prevalence of 0.5-1% [1,2]. Prevalence of RA in the Kenyan population is unknown but projections based on studies done throughout the continent estimate the prevalence to be around 0.43% [3].

In the list of conditions ranked according to the amount of disability attributed, RA sits at number 42 with a global economic burden of 5.8 billion U.S. dollars annually[4].

Apart from the economic impact, RA has been noted to cause increased mortality mainly through cardiovascular disease. This increased risk is postulated to be due to vascular damage associated with inflammation seen in the disease. An increased risk of development of lymphomas, skin cancer and lung cancer (perhaps due to the shared risk factor of smoking) has also been noted[1].

A 2003 World Health Organisation (WHO), report on medication adherence observed that improving adherence to

medical treatment may have a far greater impact on improving population health than any advance in specific treatments. This report also estimated the adherence level in non-communicable diseases to be at 50% [5].

Non-adherence to chronic therapies is rampant and costly. Estimates suggest that it costs 300 billion U.S. dollars annually and leads to the need for formulation of new therapies when existing treatments are shown to be ineffective yet the problem is not in the medication as such but rather in the adherence to treatment regimens. Aside from the economic impact, non-adherence also leads to reduced quality of life and relapses[4,6]. It has been noted as well that upto a third of all hospital admissions can be attributable to medication non-adherence [7].

The need for consistent therapy is highlighted by eight out of ten patients developing joint malalignment and almost half noted to have reduced work capacity within ten years of disease onset[2,8]. While early diagnosis and treatment prevents disease progression in upto 90% of patients, once significant joint damage has accumulated it leads to permanent disability such that even achieving clinical disease remission then does little by way of improving functional status. Permanent disability is caused more by cartilage than bone damage[2].

The level of adherence to RA treatment in the Kenyan population is not known. It is well known that DMARDs facilitate achievement of remission in upto 90% of patients[2]. Despite an increase in utilisation of DMARDS, remission rates in Kenya have remained low as was found in a 2009 study by Owino *et al*[9]. From 60 patients recruited 46.7% of patients were on DMARDs yet 88% were found to have active disease[9]. Ndirangu *et al*[10], in 2016, found that while 86.5% of patients were on DMARDS 56-65% still had active disease. In a 2017 study at KNH, Olago-Rakuomi *et al*[3] found that in spite of a majority of patients being on DMARDS (86%) most of the patients still had active disease with only 3% having achieved remission. Non-adherence may be a reason for the incongruence between DMARD therapy and disease activity seen in our setup. It is therefore important to study treatment adherence to discern the cause of this discrepancy.

Progression of RA has been linked to increased clinical disease activity. Sub-clinical inflammation as seen by imaging modalities such as ultrasound has not been shown to cause disease progression[1].

Clinical assessments include joint counts (swollen and tender), global assessments of functioning (patient's and physician's) and inflammatory biomarkers (Erythrocyte Sedimentation Rate and C-Reactive Protein). These are then aggregated in various permutations to form clinical indices such as the Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI), Health Activity Questionnaire and the Disease activity score 28 (DAS28), among others. These tools are indispensable in the treat-to-target strategy employed in the management of rheumatoid arthritis where the goal is disease remission.

In the Kenyan population Ndirangu *et al*[10] found, in a sample of 106 patients, a median Clinical Disease Activity Index (CDAI) score of 11.0 which was indicative of moderate disease activity. They also found that only 10% of patients were in remission.

A systematic review by Li et al [11] in 2017 looked at the correlation between adherence and disease activity. They included seven studies with a total sample size of 1963 patients and found a significant difference in Erythrocyte Sedimentation Rate (ESR) and tender joint count, both indicators of active disease, between adherent and non-adherent patients. They concluded that RA patients with higher adherence have lower disease activity.

The level of adherence to RA treatment in the Kenyan population is unknown. Despite increase in utilisation of DMARDS, remission rates in Kenya have remained low as was found in a 2009 study by Owino *et al*[9]. From 60 patients recruited 46.7% of patients were on DMARDs yet 88% were found to have active disease[9]. Ndirangu *et al*[10], in 2016, found that while 86.5% of patients were on DMARDS 56-65% still had active disease. It is well known that DMARDs facilitate achievement of remission in up to 90% of patients[2]. Non-adherence may be a reason for the incongruence between DMARD therapy and disease activity seen in our setup.

Materials and methods

Study design: We carried out a questionnaire based descriptive cross sectional study.

Study site: The study was carried out at the Kenyatta National Hospital's (KNH) Rheumatology Outpatient Clinic (ROPC) in Nairobi, Kenya. KNH is one of two national referral hospitals in the country and runs its specialised rheumatology clinic every Thursday afternoon. New patients are seen by consultant rheumatologists from KNH and the University of Nairobi while patients on follow-up are seen by University of Nairobi Internal Medicine residents in consultation with the rheumatologists.

Study population: This consisted of patients with a diagnosis of rheumatoid arthritis based on the American College of Rheumatology attending the ROPC at KNH.

Patient selection

Inclusion criteria: We screened patient records for adult male and female patients with a diagnosis of rheumatoid arthritis on file. They also had to have been on active treatment consisting of at least one DMARD and been on follow up for at least three months. Patients should have been able to fill the questionnaire in English or Kiswahili or be accompanied by an individual who could aid them in this. Qualifying patients who gave informed consent were included in the study.

Exclusion criteria: Any patients not fulfilling any of the above criteria.

Sample size estimation: Given a population of 125 patients (N) with a diagnosis of RA attending the KNH ROPC and using an estimated adherence rate (p) of 65% 19, the estimated sample size (n) was calculated using the Fischer's equation and was found to be a minimum of 95 patients.

Sampling method: We carried out consecutive enrollment of patients who fulfilled the inclusion criteria until sample size was achieved.

Clinical methods: The principal investigator and a trained research assistant extracted relevant data from the patient file onto the study form and thereafter administered the CQR to eligible patients. Thereafter a clinical exam was conducted which entailed examining the patients peripheral joints for swelling and tenderness as well as obtaining a patient and physician global assessment of functioning. These measures were then used to fill in the clinical disease activity index part of the study form.

Study instruments: The study instruments that were used include the CQR-5 which is an abbreviated form of the only questionnaire validated in assessing adherence in rheumatoid arthritis, the CQR-19. It is a 5 item tool with responses ranked on a likert scale from 1- completely agree to 4-completely disagree. It consists of questions 2,3,5,6 and 17 of the CQR-19. The tool was translated into the Kiswahili language using the forward and back translation method by a professional translation service located in Nairobi.

The Clinical Disease Activity Index (CDAI) was used to assess disease activity. It has 2 objective parameters consisting of the swollen and tender joint counts each out of 28 and 2 subjective parameters including the physician global assessment of function as well as the patient global assessment of function each of which is scored out of ten. The total out of a score of 76 is used to grade disease activity. This score does not require measurement of an Acute Phase reactant and has been shown to be comparable to the SDAI (Simplified Disease Activity Index) and DAS-28 (Disease Activity Scale) in assessing disease activity[9,12]. Demographic data and clinical characteristics were extracted from patient files.

Ethical considerations: Patients were recruited upon giving informed consent by signing the informed consent form. The study was undertaken after obtaining approval from the Ethics and Research Council of the University of Nairobi and Kenyatta National Hospital.

Data analysis: Data was checked for completeness and free of error prior to entry into Microsoft Excel 2017 spreadsheet. Thereafter it was exported to the Statistical Package for Social Sciences version 23.0. Demographic and clinical characteristics of the patients that are categorical were analysed as frequencies and percentages, while the continuous data was analysed as means with standard deviation or median with interquartile range. The CQR5 score was calculated out of 20 with a score of 16/20 and above indicative of adherence and a score below 16 indicating non-adherence. The level of adherence to RA treatment among patients was calculated as a proportion of those adhering over the total sample size and reported as a percentage. Clinical disease activity according to CDAI score was assessed as follows; a score of 0.0 to 2.8 indicates remission, 2.9-10.0 low disease activity,10.1 to 22 moderate disease activity and 22.1 to 76.0 high disease activity. CDAI grades were analysed as frequencies and percentages. The link between RA adherence and clinical disease activity was analysed with the use of Chi-square test while the link difference in mean CDAI scores between adherent and non-adherent groups was assessed using the independent Student t test. The predictors of adherence were analysed with the use of Chi-square tests for categorical data, and with independent Student t-test for continuous data, to compare between adherent and non-adherent groups.

Results

Ninety seven patients were recruited into the study after exclusion of three patients out of 100 screened who declined to give consent.

Socio-demographic characteristics: Table 1 shows the sociodemographic characteristics of the sample population of 97 patients. The mean (SD) age was 53.9±15.4 years with a range of 22-82 years. Majority of the patients were female; 82 (84.5%). Married patients formed 60.8% of the study population. Patients whose residence was primarily rural were 58.8% and 94.8% of patients had at least attended primary school.

Clinical characteristics: As demonstrated in Table 2, comorbid conditions were present in more than 79 patients with the median number of comorbidities (IQR) being 2 (2-3). Rheumatoid factor was positive in 96.9% of patients while 52.6% were positive for Anti-CCP and 4.1% were Anti-Nuclear Antibody (ANA) positive. Both RF and Anti-CCP were present in 48.4% of patients. ANA was positive in 5 patients, 4 of whom were RF positive and 1 was anti-CCP positive.

Only five patients were on DMARD monotherapy, while a majority of the patients, 68, were on dual therapy. Five patients were on biologic DMARDs with all of them taking conventional DMARDs concurrently. Methotrexate was the most commonly prescribed DMARD at 93.8%. The number of medications used by each patient ranged from 2-9 with a median of 6.

Level of adherence to DMARD therapy: The main objectives of the study were to determine the levels of adherence to therapy and disease activity among patients

Table 1: Socio-demographic characteristics

Variable	Frequency (%)
Sex	
Male	15 (15.5)
Female	82 (84.5)
Age in years	
Mean (SD)	53.9 (15.4)
Min-max	22.0-82.0
Marital status	
Single	38 (39.2)
Married	59 (60.8)
Primary residence	
Rural	57 (58.8)
Urban	40 (41.2)
Level of education	
None	5 (5.2)
Primary	35 (36.1)
Secondary	34 (35.1)
Tertiary	23 (23.7)

Table 2: Clinical characteristics

Variable	Frequency (%)
Number of comorbidities	
Median (IQR)	2 (2-3)
Seropositivity	
Anti-cyclic citrullinated peptide antibody (Anti-CCP)	51 (52.6)
Rheumatoid factor	94 (96.9)
Anti-nuclear factor	4 (4.1)
Class of DMARDS	
Conventional	92 (94.9)
Both	5 (5.1)
Type of DMARDS	
Methotrexate	91 (93.8)
Hydroxychloroquine	73 (75.3)
Leflunomide	33 (34.0)
Sulfasalazine	9 (9.3)
Rituximab	2 (2.1)
Tofacitinib	2 (2.1)
Adalimumab	1 (1.0)
Total number of DMARDS	
Median (IQR)	2 (2-2.5)
Total number of medications	
Median (IQR)	7 (6-7)

Table 3: Assessment of adherence to RA drugs using CQR-5 tool

Variable	Frequency (%)
Adherence level	
Mean score (SD)	15.8 (1.7)
Min-max	13.0-20.0
Category, n (%)	
Adherent	48 (49.5)
Non-adherent	49 (50.5)

Table 4: CDAI

CDAI	
Mean (SD)	17.8 (4.3)
Min-max	4.0-29.0
Grade, n (%)	
Low	5 (5.2)
Moderate	85 (87.6)
High	7 (7.2)

Table 5: Association between disease activity and adherence to DMARDs

Variable	Adherence status		OR (95% CI)	P value
	Adherent (n=48)	Non-adherent (n=49)		
CDAI				
Mean score (SD)	17.1 (4.5)	18.6 (4.0)	-	0.082
Grade, n (%)				
Low	3 (6.3)	2 (4.1)	1	-
Moderate	41 (85.4)	44 (89.8)	0.6 (0.1-3.9)	0.612
High	4 (8.3)	3 (6.1)	0.9 (0.1-9.2)	0.921

Table 6: Correlation between clinical and demographic factors and adherence to DMARD therapy

Variable	Adherence status		OR (95% CI)
	Adherent (n=48)	Non-adherent (n=49)	
Sex			
Male	9 (18.8)	6 (12.2)	0.60(0.20-1.85)
Female	39 (81.3)	43 (87.8)	
Mean age in years (SD)	52.3 (13.7)	55.5(16.8)	-
Age group			
Old (>62)	10	20	2.62
Young (<62)	38	29	
Marital status			
Single	15 (32.2)	23 (46.9)	0.51 (0.22-1.17)
Married	33 (68.8)	26 (53.1)	
Residence			
Rural	27 (56.3)	30 (61.2)	1.22(0.55-2.76)
Urban	21 (43.8)	19 (38.8)	

Variable	Adherence status		OR (95% CI)
	Adherent (n=48)	Non-adherent (n=49)	
Level of education			
Below primary	19	21	1.14(0.51-2.57)
Above Secondary	29	28	
Comorbidities			
Median number (IQR)	2 (2-3)	2 (2-3)	-
DMARDS			
Median number (IQR)	2 (2-2.5)	2 (2-2)	-
Total medications			
Median number (IQR)	6 (6-7)	7 (6-7)	-

with rheumatoid arthritis attending the KNH ROPC. Table 3 demonstrates that the overall adherence level we found; as a proportion of those patients who scored more than 16/20 on the CQR-5, was 49.5%.

Clinical disease activity: Clinical disease activity scores as shown in Table 4 demonstrate a mean (SD) CDAI score of 17.8 (4.3). Most patients were classified as having moderate disease activity (87.6%) while 5.2% and 7.2% were found to have low and high disease activity respectively. None of the patients were found to be in remission.

Correlation between CDAI and adherence to DMARD therapy: Chi square test was used to analyse the correlation between CDAI grades and adherence to DMARD therapy. Odds ratios (p values) of 1.0, 0.6 (0.6) and 0.9 (0.9) were obtained for low, moderate and high disease activity respectively showing no significant difference between adherent and non-adherent groups. However an independent student t test run to compare the mean CDAI values between adherent and non-adherent groups was found to trend towards significance with a p-value of 0.08 as shown in Table 5.

Correlation between clinical and demographic factors and adherence to DMARD therapy: We found a significant difference in adherence between patients aged less than and more than 62 years with the younger group having a higher level of adherence (OR 2.62 p 0.036). No other significant correlation was found between clinical and demographic factors between patients who were adherent to and those that were non-adherent to DMARD therapy. However, there was a tendency toward significance (p=0.11) when comparing adherence between single and married patients with the latter having a higher level of adherence. This is demonstrated in Table 6.

Discussion

The main objective of this study was to determine the levels of adherence to DMARD therapy in a representative group of patients with RA attending the KNH ROPC and explored the relationship between adherence disease activity and other patient characteristics. Socio-demographic trends indicate that the RA population in Kenya is getting older. The average age of patients in our study is 54.9 years which is in keeping with a trend of increasing patient age from a mean of 41.4 years in the year 2007, 48.7 years in 2016, 50 years in 2017 and 50.7 years in 2020[3,9,10,13]. This trend can have both a positive and negative connotation. It could indicate that RA patients are living longer due to better management of their disease hence being on follow-up for a longer time. On the other hand it could indicate that there is a delay in diagnosis of patients who are then predisposed to having more severe and advanced disease at treatment initiation.

The female to male ratio of our study population; 5.4:1, this more in keeping with global trends of 3:1 compared to previous findings in Kenya which showed a much higher female to male ratio of around 9:13 [9,10]. This change could be indicative of a shift toward increased health seeking behaviour among Kenyan men leading to a higher number being diagnosed with RA.

A higher proportion of patients was found to be rural dwelling than urban; 58.8%. This demographic characteristic has not been previously studied in our population hence we are unable to make a comparison. There was no significant difference in adherence to treatment between the two groups.

There was a trend toward significance (p= 0.11) when comparing single and married patients' levels of adherence with the former noted to be at a higher risk of non-adherence. This is in keeping with findings made in a systematic review of adherence to methotrexate therapy in RA whereby cohabitation was found to be a significant predictor of adherence [6].

A departure from previous local studies is the finding that there has been introduction of biologic DMARDs (5 patients) into the treatment repertoire with previous studies noting no usage of bDMARDs among study participants[3,9,10]. This is an encouraging finding given the low remission rates our population has demonstrated. However increased numbers would be needed to assess

the efficacy of these medications compared to the conventional DMARDS in attaining remission.

The level of adherence to DMARD therapy varies widely depending on many factors among them the tool used, patients' demographic and clinical characteristics. The most reliable indirect measure of adherence among patients with rheumatologic diseases remains the Compliance Questionnaire for Rheumatology-19 and we used an abbreviated and validated version of it; the CQR-5.

The total sample size obtained was 97 patients with 48 patients scoring higher than 16 out of 20 on the CQR-5 giving us an overall adherence rate of 49%. The mean CQR-5 score (SD) was 79.0% (70.5-87.5); an important benchmark to which future scores can be compared for a measurable assessment of improvement or reduction in the level of adherence.

Global averages for adherence are around the 66% mark[15] which puts our patient population at a much lower level of adherence. This was an expected finding given this population's historic tendency to have high disease activity[3,9,10,13]. While similar studies conducted in Africa are scarce to find, one carried out in Egypt demonstrated an adherence level of 65% [14].

While the adherence level found in our population was lower than global averages of 66% many studies have found even lower adherence levels. Prudente *et al*[8] found an adherence level of 16.4% in their sample of 55 Brazilian patients with rheumatoid arthritis. They found a duration of therapy longer than 15 years and the presence of more than six comorbidities to be associated negatively with adherence[8]. This indirectly coincides with our finding of patients who were on more than 6 drugs having a tendency toward non-adherence (p=0.184). This perhaps could be explained by the increased cost of drug acquisition and other difficulties associated with an increased pill burden.

Wabe *et al*[15] found a lower level of adherence at 27.3% among their sample of 110 patients with RA in Australia. This is much lower than that of our population (49.0%) however the median CQR score of 71-73% was comparable to that of our population's (79.0%). The only significant socio-demographic factor found to be associated with adherence was older age (>62 years). Similarly, we found a significantly higher level of adherence among patients younger than 62 years compared to those who were older (OR 2.62, 95% CI 1.07-6.45, p=0.033). This difference could perhaps be explained by this group of patients having a higher level of education than the older group with 54 patients having attained higher than primary education in the younger age group compared to three patients in the older age group[15].

Many studies, however, found a higher level of adherence. A study on 96 RA patients in France using the CQR-19 found an adherence level of 59%. All patients were on methotrexate with 57% also on biologic DMARDS. This is in stark contrast to our patient population where a minority were on bDMARDS (5.1%)[16].

A 2021 study on 88 rheumatoid arthritis patients carried out in Saudi Arabia using the CQR-5 found an adherence level of 84.1% [17]. In both the French and Saudi studies a pharmacist led counseling session was available, an amenity absent in our setting.

We used the CDAI to assess the level of disease activity. Studies undertaken at the same setting by Olago-Rakuomi *et al*[13], Ndirangu *et al*[10] and Jayant[13] found active disease in 97.0%, 90.4% and 97.2% respectively. While the number of patients in remission were few in those studies no patient in our study was in remission and while a conclusive answer is beyond the scope of our study it could be postulated that due to closure of the follow-up clinics due to Covid-19 safety protocols some patients may have fallen behind in their management. This factor may also have contributed to the overall low adherence level of our patients.

While no difference in adherence to DMARD therapy was found between groups with high and low disease activity, we did encounter a trend toward significance when comparing the mean CDAI score between the adherent and non-adherent groups (p-0.08). Perhaps with a larger sample size this difference may have been significant. This finding does indicate that poor adherence may be contributing to the high disease activity in our population of RA patients.

Conclusions

Adherence to DMARD therapy and disease activity among RA patients attending the KNH ROPC were determined using simple and effective tools. The adherence level was lower than global averages and WHO recommendations while disease activity was high. No significant association was found between adherence and patient factors. Closure of the clinics due to Covid-19 containment measures may have contributed to these findings. Enhanced patient follow-up, setting up of clinics in rural areas for improved accessibility and employment of rheumatology nurses may improve adherence.

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Individuals' perspectives on the impact of living with lupus in Kenya

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Abstract

Background: Lupus is a chronic, autonomic, multisystem disease that predominantly affects women of child bearing age. Lupus has both physical and psychosocial impact on affected individuals. There is paucity of data on the impact of living with lupus and the self-management strategies employed by affected individuals in Kenya.
Objective: To explore how living with lupus has affected the individuals' lives and identify their self-management strategies.
Design: A generic qualitative approach with principles of constructivist grounded theory.
Setting: Two rheumatology clinics in Nairobi, one private and one public health facility. Ethical approval was obtained from the relevant institutional ethical committees.
Methods: Participants were identified using purposive and theoretical sampling techniques. Face-to-face interviews were conducted. Interviews were transcribed verbatim and analyzed inductively using the constant comparative method.
Results: The study identified a key category of "a shadow of myself" and three sub-categories; i.e. loss of self, biographical disruption and biographical reconstruction. The findings revealed that the illness disrupted individuals' lives in various ways. However, they attempted to reconstruct their disruptions with variable success.
Conclusion: The study revealed that living with lupus was disruptive to individuals who previously had ordered lives and the need to support them, for meaningful life reconstruction.

Key words: Lupus, Individual perspective, Impact

Introduction

Lupus is a chronic autoimmune disorder affecting more than one organ. It is characterized by various clinical manifestations which are consequences of widespread inflammation in numerous organs of the body such as the skin and mucous membranes, joints, kidney, lungs, heart and occasionally the gut[1]. Skin involvement is present in 80% of the patients and comprises of skin rash, photosensitivity, hair loss and painful mucous membranes. Patients may also present with musculoskeletal features giving rise to painful or swollen joints and bone necrosis. Haematological effects may include anaemia, low platelets and formation of auto-antibodies. Patients may also present with cardiopulmonary features which may include hypertension and chest pain. Renal disease, neuropsychiatric features, eye problems and gut involvement may also be present[2]. Although skin and musculoskeletal manifestations are the most common symptoms, lupus may present in variable combinations of clinical features as organs may be involved separately or in combination. Most people with lupus have variable symptoms and an unpredictable course and prognosis[3,4] indicates that chronic illness can be episodic or continuous, and the body's response may be visible or invisible, and may include the experience of intrusive symptoms like pain and fatigue[5]. Pain stands out as a symptom of chronic condition[6]. Lupus appear at a younger age when one is most active in terms of educational achievements, paid work and raising families. Individuals with lupus not only complain of pain but also bewildering fatigue, persistent fever, malaise and weight loss[2], depriving them of their previously taken for granted continuity of life[7].

The experience of living with chronic illness presents both personal and social challenges which may have life-long implications. In addition, Heydari *et al*[8] reported that non-communicable diseases are the leading cause of morbidity and 86% of all deaths globally. Charmaz[4] also states that chronic illness causes more social, interactional and existential problems because of being long-term. The illness may incapacitate the individual and cause a permanent alteration to their way of life, necessitating re-evaluation of

functional abilities in their social world[9]. Chronic illness, therefore, impacts on individuals in profound and various ways, and the lived experience often includes different forms of physical and psychological impact. The purpose of this study was to explore how living with lupus has affected the individuals' lives and identify their self-management strategies.

Materials and methods

This was a qualitative research which utilized a generic qualitative approach and principles of costructivist grounded theory. The research sites were at Kenyatta National Hospital and Mater Hospital where there are rheumatology clinics. Ethical approval was sought from the University of Nairobi/Kenyatta National Hospital and The Mater Misericordiae ethics and research committees respectively. Study participants were purposively and theoretically sampled. Data collection was conducted following informed consent, through face to face in-depth interviews, using an interview guide. The data was coded and analyzed by constant comparative method and thematically.

Results

Twenty-one individuals with confirmed lupus diagnosis were recruited. Eleven were from Mater Hospital which is a private hospital while the other ten were from Kenyatta National Hospital rheumatology clinic which is a public hospital. The participants' ages ranged from 19-56 years with a mean age of 34 years (SD 9.2). Majority were between 21-40 years with only one patient above 50 years of age. Majority (n=19) had achieved high school education and above but only 5 of them were in employment. In addition, about 75% of the participants were above 30 years of age and not married (Table 1).While exploring how living with lupus had impacted individuals' lives,'A shadow of myself', a phrase used by one of the participants emerged as a theme from the data. The phrase summarized her life as she described herself as a different person from the person she used to be:

'There is no joy, you know?... All the time you are thinking about the condition no matter how strong you have grown…I am no longer what I used to be. I am just a shadow of myself… ' (ID 07, PRI)

'A shadow of myself' fitted other participants descriptions of themselves too and comprised of two sub-themes: loss of self and biographical disruption.

Table 1: Demographics

Characteristic	Participants (public hospital)	Participants (private hospital)	Total
No.of participants	10	11	21
Gender			
Male	0	1	1
Female	10	10	20
Age (years)			
Under 20	0	1	1
21-30	5	2	7
31-40	3	6	9
41-50	1	2	3
51-60	1	0	1
Highest level of education			
Primary	1	1	2
High School	6	0	6
Vocational	1	2	3
Qualification			
Diploma	0	3	3
University degree	2	5	7
Marital status			
Single	8	7	14
Living with partner	2	4	6
Employment status			
Employed full time	4	7	11
Unemployed	5	3	8
Student	1	1	2

Loss of self

Loss of self is a phrase[4] which first used in her study of individuals with chronic illness. In this study, all participants described experiencing negative physical changes, some of which were invisible while others were visible. The invisible symptoms included pain, fever and fatigue, with pain and extreme fatigue being the most frequently mentioned. For example:

'Am a teacher by profession, but from 2011… up to date, I have not gone to work… I could feel a lot of pain... It would take me about a week experiencing a lot of pain… and then it would shift... I have not been able to do anything. Writing on the chalk board is a problem. I can do it for one second then my hand refuses.' (ID 02, PRI)

The pain seemed to last for long durations which made her suspend her teaching job. Some participants also reported that the pain they were experiencing was also interfering with the quality of sleep and work:

'And at times you wake up with so much pain. You are willing to do something, but your body cannot let you do it. As much as my heart is willing, it is not easy..'(ID 13, PUB).

The narrative of this participant indicated that the pain had no trigger because she would wake up in pain even before engaging in her daily activities. Also, the pain would limit the quality of her activities. About half of the participants spoke of having no strength due to a new sensation of feeling exhausted all the time:

'The first feeling I had was tiredness; extreme fatigue... the one that I really felt was this sort of fatigue that I could not account for… fatigue that came out of nowhere because I had always been a somewhat active person.' (ID11, PRI)

It is evident that the tiredness experienced was new and intense, incapacitating and also unrelated to activity as it started in the morning. The participants acknowledged that fatigue frequently compromised their physical functioning and affected their work output.

The visible negative changes that participants experienced included weight loss or weight gain, hair loss from the head and rashes on the body. About a quarter of participants mentioned that they experienced weight loss. Additionally, about half of the participants reported having loss of appetite, while others reported having mouth sores. Some participants also reported negative reactions from other people:

'My weight started to reduce. It took about one year before I was diagnosed with lupus. When I eat,I vomit. That is another challenge…You hear people saying I have HIV...That is because of the way I appear. '(ID12, PUB)

Most participants who had lost weight were unhappy with their body image and found talking about it very distressing as they emphasized how much the weight loss had changed their outward appearance and threatened their femininity. Some participants seemed to suggest that their social contacts associated their weight loss with having HIV infection. Coping with weight loss was often not easy as some participants admitted that the negative body image depressed them and they stopped socializing and preferred not to go out. Besides experiencing weight gain or loss, hair loss and having skin rashes were also major contributors to some participants' negative views of their changed body image. The affected individuals understood that there was a change in their former self-image:

'I started getting a velvety, dark kind of rash over here [pointing across the face]. The butterfly rash had occurred so when I went to the office, one guy told me "… just go to the hospital. This looks really bad."' (ID10, PRI)

The changed body image due to skin rashes made the individuals with lupus feel different compared to their previous physical appearance.

Feelings of emotional distress was also attributed to loss of self. Some participants described feeling anxious and depressed by using words like 'I am emotionally distressed', 'feeling very depressed' and 'very worried'. The effects of illness which caused emotional distress to some participants included: changed physical appearance, loss of health, side effects of some lupus medications, fear of death and lack of social support:

'… Sometimes you have the butterfly rash, and it is so bad, and you know, you see people looking at you, and of course giving you all sorts of labels. They are not talking about it, but you can physically see from their facial expressions - you can really gather a lot. I had lost so much weight. My clothes are not fitting me, and I am emotionally distressed...' (ID 07, PRI)

This narrative illustrates that the changed physical appearance was stressful to the participant because of the responses her changed appearance elicited. She experienced loss of self-esteem and impaired self-image. The impact of changed physical condition associated with the interference to physical and social activities and the impact of emotional distress caused disruption in various areas of the participants' lives.

Biographical disruption

The second sub-category that emerged has been termed 'biographical disruption', a concept first described by Bury. This sub-category fitted the data because it summarized the descriptions the participants used to express the extent to which they experienced lupus as

biographically disruptive to their formerly organized lives and relationships. Participants described disruptions in their work, career, finances, family and social relationships including their marital lives, making Bury's concept of biographical disruption relevant.

Some participants described having functional impairment related to their ability to perform daily household or workplace tasks due to joint pains and feeling weak. For example:

'... I have become weak. I have become very weak. There are some things I used to do that I cannot do anymore. I would go to the market and buy even four duvets and carry them myself. But now, sometimes I get to a point where I cannot even open a water bottle or peel off a tangerine. I cannot flush the toilet. It has changed my life ...'(ID 20, PUB)

Participants became aware that their level of doing things was greatly diminished compared to the past. They had to make decisions regarding what activities they could perform which was restricting their lives. It was noteworthy that the tasks the women highlighted as not being able to perform were female gender related chores in the traditional African context, such as going to the market and washing clothes. Having lupus also affected the performance of some participants' paid employment. For example, one participant indicated:

'I used to work as a tailor, but I stopped because I cannot even cut something. So, I do nothing.'(ID 12, PUB)

This participant became aware that she could no longer use her hands to work as a tailor, which is a technical job, and she had to give up her source of income altogether. Having lupus took away her financial independence. Another participant described how having lupus caused a strained relationship with her employer:

'They feel I'm too weak to work. I'm a person in the public-relations department, I need to move about. But I'm fighting them about it…. It was a very big case because she went ahead and failed to renew my contract which expired last month. And I told them I was not signing any exit form because of being sick… "(ID 20, PUB)

Having lupus also seemed to have worsened the financial status of some participants due to expensive healthcare costs and their compromised ability to engage in paid work. Some participants had already used their family finances to meet the huge medical bills, which meant that they had run out of family finances:

'*Ya. It had such impact, because we had already spent a lot. We had taken some loans, and eventually we had to have a fundraising. So, part of that helped us to fund my treatment until again this year, we started feeling the pinch because drugs are very expensive... You run out of money, but we thank God we have managed.' (ID02, PRI)*

The study therefore established that having lupus significantly impacted on household and workplace responsibilities. It also negatively affected the participants' financial situation. Some participants also commented on how having lupus reduced their capacity to participate in family life thus disrupting their married life and parenthood:

'... Although you haven't asked me, lupus affects your intimate relationship with your husband seriously because you are always cagey. Today it's the back, tomorrow it's another thing. People don't even understand, they think you are always complaining… So, one, it affects your intimacy with your husband seriously. You no longer have any joy in anything. At the end that strains the relationship… And so, you have to put a lot of effort in everything because sometimes you really don't want to be intimate. '(ID 07, PRI)

In the narrative, the participant's use of the words "and so you have to put a lot of effort in everything" brings out the subordinate role of women in marital relationships, and the difficulty they have in making decisions. In this study, it was also established that about three quarters of the participants were single with only one of them stating that she had been married before and got divorced. She expressed that having lupus was the primary cause of her divorce:

'... I was married to someone at that time. This person did not show any interest or any concern for what I was going through… when I told my husband that I had lupus, he cheated on me with someone else, and he walked out on the relationship, leaving me alone. So, I became single.'(ID 13, PUB)

While another participant stated that she discouraged the start of relationships by pushing away those who showed interest in her. She saw her illness as a barrier, yet this could have been a way of being very realistic about the possible effects of lupus on marital life. There were those who also seemed to have either postponed marriage or having a family:

'... Let me say… there is a time I wanted to get married, but when I fell sick, I lost interest completely.'(ID 12, PUB)

'Yeah. In fact, when I meet someone, I tell them, "You are just getting yourself into a burden. This is a sick person". ... In fact, I just shut them down from there. I just don't want to be in that relationship'. (ID 17, PUB)

'The only other thing that I wish I could do but I cannot is, say, to have children. I would like my daughter to have a brother or a sister. However, I cannot have children due to the medication that I take..'(ID 10, PRI)

From the narratives, it is evident that getting married or having children was an issue that some participants dealt with. They were either doubtful about getting

married and having children because of the unknown consequences, or they seemed to have made a decision against getting married due to their condition.

Disrupted relationships were also mentioned regarding family and other social relationships. More than half of the participants indicated that their illness caused deterioration in their family relationships. For some, the precarious financial situation was the source of the strained relationship:

'... He [husband] had left in the morning; I was thinking that he was coming back. I waited for him in vain until ten o'clock. So, I knew he had already gone and switched off his phone. I called my brother and borrowed five hundred shilling from him.' (ID 05, PUB)

Two other participants expressed how they were not playing their parental role as they should have. For example:

'... Of course, rearing of my children. The whole of last year, I literally did nothing to my children. The way the child comes, you want to hold them and I cannot… The way children want to be happy with their mother; I cannot be happy with them… As far as the area of rearing my children, I feel I have been quite inadequate.' (ID 02, PRI)

The findings also revealed that there were participants who were avoiding getting into relationships due to their fears and due to their past experiences:

'Yeah. It has affected how I relate to people. I just don't want people to be close to me. I feel like when they find out they are going to reject me...'(ID 17, PUB)

'Even socially there are friends I used to see, and yet when I hear they want to be somewhere, I do not want to go... I don't want to meet them because what am I going to discuss with them? ... There is no news. So, socially, it also affects you. It has affected me and that is my greatest problem... You think the world is beaming you, right?' (ID 07, PRI)

This group of participants seemed to acknowledge their role in the strained relationships and the resulting constrained lives and social isolation. The participant (ID 07) feared to get into a relationship because of the experience she had with her friends before.

On the whole, having lupus disrupted various aspects of the participants' day-to-day activities, especially regarding paid work which affected their finances. It also impacted their house work, family life and social relationships.

Discussion

On the whole, patients in this study felt that the disease made them experience numerous forms of loss such as: loss of their previous body image with the associated experience of humiliation; loss of productive function both at work and at home; loss of financial stability which affected their economic resource; loss of social and family stability with associated strained relationships and the experience of emotional distress. The individuals' sense of loss fitted with Charmaz's[10] concept of 'loss of self' which she refers to as a combination of the loss of self-identity and self-esteem. According to Charmaz[10], the self is social in nature and is developed through social relationships. Also, she indicates that "experiencing illness is a social-psychological process in which the inner dialogue between the I and the me changes and definitions of the experience change"[10]. Charmaz[10] argues that loss of self is experienced by people with chronic illness because the illness changes their former activities and lives, and that the loss of self can be continuous, a view which was also evident in this study.

On the other hand, Bury's[11] theory of 'biographical disruption', which refers to functional restrictions brought about by chronic illness, was also a good fit for discussing patients' perceptions regarding impact of the illness. Most participants were no longer able to carry out most of their former activities of daily living, whether inside or outside the home. This was mainly due to the new body sensations they experienced, like pain and fatigue. Bury's[11] work brought into focus the meaning of illness for the individual. The study acknowledged that disruption arises because the illness disorganizes people who had taken for granted live and the social world in which they live.

Lupus also fits well with Bury's[11] biographical disruption theory because it is an illness that starts in adulthood and disorders a previously ordered life. This is in line with Williams'[12] criticism. Williams suggested that Bury's biographical disruption was only applicable to people who were previously active and productive, but not to children and the elderly. In this study, patients' ages ranged between 19-56 years and their previously active lives had been disrupted in one way or another. Job loss was noted to be mainly high among those who were not in skilled employment and those with jobs that required high physical demands. In contrast, those who were in positions of responsibility were considering early retirement. Other studies have also emphasized that lupus can diminish an individual's capability to work, with an end result of having work disability and/or changes in the nature of an individual's work. Similar to this study, Yelin *et al*.'s[13] study established that job loss was higher among those who had no high school education. Also, those who had early onset of lupus, or a longer duration

of lupus, negatively experienced high physical and high psychological demands of the job.

In this study, some patients also described how they felt that their female gender roles - child bearing, rearing and doing housework - were disrupted by lupus, which disproportionately affects women. Some women decided to remain single or had no children by choice. Some wondered if they ever will be able to get married and have children, while others implied that they could no longer have more children despite their desire to have more. These findings were similar to other studies that involved women with other chronic diseases[14,15]. 'Gender role' is a term which denotes a society's expectations of how men and women should behave. This is learnt during the socialisation process from birth through family, education, peer groups and the mass media[16]. In traditional African society, the acceptable roles and behaviour of both men and women in a family and community are culturally defined along femininity and masculinity lines[17]. Males are endorsed as decision makers, which is alleged to be in the best interest of the family[18]. Also, women are expected to act according to decisions made by their husbands or by a male family leader. Participants in other studies from West Africa and India argue that the role division which gives men a higher status than women is not in the best interest of the family, and is therefore a form of gender discrimination[19]. However, literature indicates that traditional gender roles are breaking down due to the shift from the traditional model of a wife as a housewife and a husband as an employed person. This is attributed to the current equal educational and economic opportunities for men and women[20], and the collapse of attitudinal and socio-cultural factors which previously acted as obstacles created by gender role stereotypes[21]. Participants in a study from Africa also attributed the breakdown to the fact that gender roles are conventional and can be altered because they are not part of a moral code[19,22]. However, some studies established that working women perceived themselves as still performing significantly more housework than men[23,24]. On the other hand, some participants in another study insisted that gender segregation in domestic work persists[24]. This was an observation which was also evident in this study. There were participants who mentioned with concern that they could no longer perform domestic chores like washing clothes and caring for their children and the expectations from the extended families. However, the study did not establish women's' concerns regarding doing more domestic chores than their male counterparts.

Therefore, this study demonstrated that similar to other chronic conditions, lupus is a condition that is regarded as disruptive, with physical and functional changes in the lives of individuals who are in the prime of their lives. The changes, in turn, affect the individuals socially, economically and emotionally. Bury[25] argues that some individuals have more control over their lives before onset of their illness than others. The view of having control over ones' life is closely related to social factors such as class, ethnicity and gender, and other determinants such as economic and biological factors.

Conclusion

The study established that having lupus was experienced as a negative turning point for all participants as most participants acknowledged that they were not the same as before the illness.

The illness remained ambiguous with insurmountable challenges. This study suggests that individuals who possessed positive social factors such as better economic, social and cultural resources had slightly better control of their lives than those who had limited resources. The study established that lupus is a particularly challenging illness to live with and that living with lupus in Kenya involved extra challenges. This implied the need to explore strategies which may be used to assist individuals to cope better with the condition.

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Rheumatologic complications of checkpoint inhibitor immunotherapy: a review

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Abstract

Background: Immune Checkpoint Inhibitors (ICIs) are currently used in the management of various cancers. However, they tend to cause adverse effects, collectively known as immune related adverse effects, (irAEs)by causing tissue damage due to immune activation.
Objective: The aim of this literature review is to address those rheumatological irAEs associated with the use of ICIs and how to manage them.
Data source: The literature review uses medical science-based literature published locally and internationally on the risk of rheumatological immune related adverse effects.
Conclusion: A spectrum of rheumatological irAEs have been linked to the treatment of various malignancies with ICIs, the most common being inflammatory arthritis. Most rheumatological irAEs can be managed successfully by use of glucocorticoids

Key words: Immune checkpoint inhibitors, Immunotherapy, Rheumatology, Arthritis, Glucocorticoids, Immune related adverse effects

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Introduction

Immune checkpoint inhibitors are a type of immunotherapy that is currently being used in the management of various types of cancers. However, they cause a myriad of adverse effects involving nearly every organ system. These adverse effects are collectively known as immune-related adverse events (irAEs). The irAEs result from tissue damage by immune activation and inflammation.

The ICIs work by blocking inhibitory molecules on T cells and tumour cells. By doing so, they enhance T cell mediated immune response towards cancer cells, leading to cancer cell death. Initially ICIs effectiveness was demonstrated in metastatic melanoma, but many indications have since been approved, including non-small cell lung cancer, renal cell carcinoma, Hodgkin's lymphoma and many other solid tumours. In this article, we review the rheumatologic complications of ICIs and their management.

Mechanism of action of ICIs

Usually, when a T cell is activated, multiple mechanisms regulate the level of activation preventing over activation of the T cell response. Tumour cells overly express these inhibitory molecules dampening and evading the immune system[1]. The major pathways that control T cell activation are binding of cytotoxic lymphocyte antigen protein 4 (CTLA-4) on T cells to CD80/86 on antigen presenting cell, and binding of programmed cell death receptor 1 (PD-1) to programmed cell death ligand 1 or 2 (PD-L1 or PD-L2). ICIs block these inhibitory pathways, allowing for increased activation of T cell with a greater response against tumours.

The first approved ICI, ipilimumab, blocks the binding of CTLA-4 to CD80/86. Other ICIs inhibit either PD-1 or PD-L1. The PD-1 inhibitors include pembrolizumab, nivolumab and cemiplimab while the PD-L1 inhibitors include atezolizumab, avelumab and durvalumab (Figure 1).

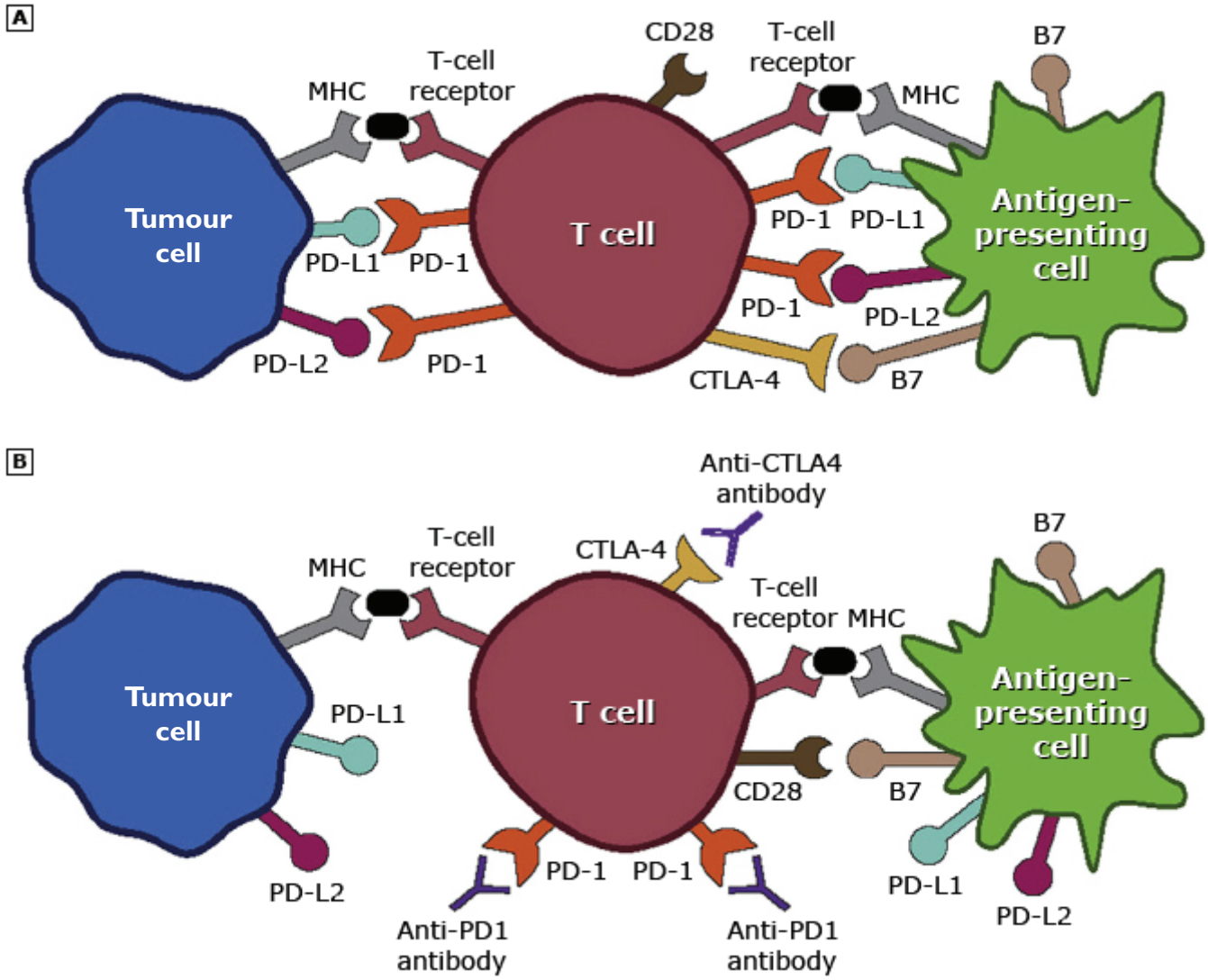
Pathogenesis of rheumatologic complications

ICIs can cause off-target tissue damage (irAEs) by non-specific activation of T cells. The clinical manifestations depend on the organ system involved, its severity and temporal relationship to ICI therapy[2].

The specific immune pathways implicated in irAEs are not yet determined. However, some data suggest that interleukin 17 and T-helper 17 (TH17) cell response may be responsible for the pathogenesis of irAEs[3].

There could be possible overlap in the pathogenesis of rheumatologic irAEs and rheumatoid arthritis. For example, abatacept which is fusion protein between CTLA-4 and Fc portion of IgG is used in the treatment of inflammatory arthritis. Its mechanism can be thought of as the converse of ipilimumab in that it blocks

Figure 1: A) PD-L1 and PD-L2 on tumour cells and APCs bind to PD-1 on the T cell, and B7 on APCs binds to CTLA-4 on the T cell.
(B) Antibodies to PD-1 or CTLA-4 block inhibitory interactions, allowing for positive costimulation (B7 binds CD28).



CTLA-4: cytotoxic lymphocyte antigen protein 4; PD-1: programmed cell death receptor 1; MHC: major histocompatibility complex; CD28: cluster of differentiation 28; PD-L1: programmed cell death ligand 1; PD-L2: programmed cell death ligand 2; APCs: antigen-presenting cells.

the activating interaction between CD28 and CD80/86, rather than blocking the inhibitory interaction[4]. Similarly, some mouse and human studies have implicated PD-1 in the pathogenesis of RA[5].

Epidemiology

The rheumatologic irAEs have been less reported in literature in comparison with other types of irAEs. The most common symptoms include arthralgia, myalgia and sicca complex[6]. The epidemiological estimates vary from 1% to 43% for arthralgia, 2% to 20% for myalgia and 3% to 24% for sicca syndrome[7]. However, the development of systemic autoimmune disease that requires rheumatological referral is less common, occurring in about 3.5% to 6.6% of the patients[8,9]. It is possible that the relatively low frequency rheumatologic irAEs is the result of failure to recognize the significance of rheumatologic disease symptoms by the treating provider, coupled with the fact that rheumatologic irAEs are rarely life-threatening and hence not graded as severe. Furthermore, it is unclear on how arthralgias actually represent inflammatory arthritis because of the different ways a given clinical symptom or finding may be coded (e.g., arthralgia, joint effusion, arthritis) for data collection. Most information of rheumatologic irAEs is from case reports.

The rheumatologic irAEs that occur include inflammatory arthritis, inflammatory myositis, sicca syndrome, vasculitis, eosinophilic fasciitis, polymyalgia

rheumatica, sarcoidosis and scleroderma[7,10-15]. The rheumatologic irAEs tend to occur more frequently in patients who are treated with ICI combination therapy and with anti-PD1/ ant-PDL1 as compared with monotherapy and anti-CTLA4 respectively[16]. In addition, 71% of patients with pre-existing autoimmune disease may experience flares or develop another autoimmune disease[17].

General principles of management

The clinical manifestation of rheumatologic irAEs varies widely. Some clinical manifestation may mirror classic rheumatological diseases while for others, the characteristic features may be absent. In addition, it is common for patients with rheumatologic irAEs to have other non-rheumatologic irAEs, hence obtaining a detailed history and thorough physical examination is important. The severity of irAEs, future cancer treatment options, tumour response, oncologist and patients' preference should all be considered in deciding treatment for the rheumatologic irAEs. It is recommended that there should be close consultation with the patient's oncologist, to determine the most appropriate intervention and whether to continue or discontinue ICI therapy.

Inflammatory arthritis

Clinical manifestation and diagnosis

Inflammatory arthritis is the most common rheumatological irAE[18,19]. It usually develops within two weeks but may be delayed up to a year of ICI initiation with joint damage occurring within months of symptom onset[9,19]. Inflammatory arthritis presents with a variety of clinical presentations ranging from small joint polyarthritis to large joint oligoarthritis to psoriatic arthritis[18,20,21]. Patients treated with anti-PD1 and anti-PDL1 are more likely to develop small joint polyarthritis as the only irAE, while those treated with anti-CTLA4 will develop large joint oligoarthritis and have had another irAE[22].

The diagnosis is primarily made clinically, based upon the history and physical examination finding of a new onset arthritis following treatment with ICI. A detailed history should be taken to rule out antecedent rheumatological manifestations and the pattern of joint involvement should be characterized. A diagnosis of ICI induced arthritis can be made in patients who do not have preceding symptoms and presence of features suggestive of classic form of inflammatory arthritis.

Laboratory studies are useful but are not necessary for diagnosis. Most patients are seronegative for rheumatoid factor and cyclic citrullinated peptide. Inflammatory surrogate markers like C-reactive protein and erythrocyte sedimentation rate may be elevated, but their utility is compromised, as these markers are also elevated in malignancy.

Plain radiographs of the affected joint should be taken at time of initial presentation more so to serve as a baseline for comparison with later studies as they may be normal during the early phase of the disease. Magnetic resonance imaging and ultrasound have shown tenosynovitis, enthesophytes and bony erosive disease[23]. This finding can be helpful in distinguishing inflammatory arthritis from non-inflammatory joint disease. Other disease conditions that present as inflammatory arthritis should be ruled out. These include paraneoplastic syndromes, polyarthralgia due to medications and bone metastasis with erosive joint changes. Bone metastasis should be suspected if there is a joint with disproportionate erosive disease or a joint that does not respond to therapy.

Treatment

Treatment of inflammatory arthritis due to an irAE is based upon case reports and case series. The treatment should be personalized based on the clinical findings and the severity of the disease. Treatment decision should be made in close collaboration with the patient's oncologist.

Treatment of mild arthritis

Mild arthritis is the involvement of few joints without any significant functional compromise. Oral Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) or low dose glucocorticoids are recommended for patients with mild arthritis. ICI therapy is usually continued. Oral NSAIDs are commonly used but some patients with very mild arthritis may also benefit from topical NSAID. There is no preference for any specific NSAID, however the drugs should be used at the lowest necessary dose and for the shortest duration needed. Patients should be monitored regularly for gastrointestinal adverse effects as ICI therapy has also been associated with gastrointestinal adverse effects like diarrhoea and colitis.

In patients whom NSAID are contraindicated or in whom a more rapid response is required, glucocorticoids like prednisone can be used. Treatment should be initiated with the lowest possible dose of glucocorticoid, for example prednisone 10mg to 20mg daily. The response should be assessed after couple of weeks and the dose adjusted to the minimal dose required for disease control. ICI therapy can be safely used concurrently with low dose glucocorticoids. Intraarticular steroid injection, similar to rheumatoid arthritis, can be administered in patients with oligoarticular disease[24].

Treatment of moderate and severe arthritis

Moderate and severe arthritis is involvement of multiple joints or functional impairment. In these patients' higher doses of glucocorticoids, for example prednisone 1mg/kg/day, may be required. ICI therapy is withheld temporarily. High doses of glucocorticoids should at least be used for a month and then tapered down to a lower dose if the

patient is responding well to therapy. ICI therapy can be re-initiated during the period of glucocorticoid tapering.

Conventional Disease-Modifying Antirheumatic Drugs (DMARDs) can be used in patients who cannot be successfully weaned off to a lower dose or entirely off glucocorticoids. These include sulfasalazine, hydroxychloroquine or methotrexate. They should be initiated in the same way as for rheumatoid arthritis[18,19]. The decision to start ICI therapy should be made on an individual basis.

In selected patients with severe arthritis who have steroid refractory disease, the use of Tumour Necrosis Factor (TNF) inhibitors has been suggested or preferred. These include patients in whom it would be undesirable to wait for several weeks for a response with conventional DMARD, or in patients in whom synthetic DMARDs is contraindicated like patients with liver disease or cytopenia. Either of the TNF inhibitors: infliximab, adalimumab and etanercept can be used. There is no preference for one over another. The precautions, dosing and strategies used for these agents is similar to those used in patients with RA and other related conditions[18,19].

The efficacy and safety of other drugs like tocilizumab is extremely limited. Tocilizumab has been used in small number of patients to treat inflammatory arthritis[25]. It is mostly recommended in patients who have contraindications to TNF inhibitors or who do not respond to with at least two months treatment of TNF inhibitors. There have been concerns about using concurrent tocilizumab and ICI, as both of these drugs increase the risk of colitis and intestinal perforation, however limited data suggests no such increased risk[26,27].

Prognosis

The development and treatment of ICI associated inflammatory arthritis does not adversely affect the tumour prognosis[28-30]. However, the arthritis may persist following discontinuation of ICI[31].

There is a theoretical concern that immunosuppressive drugs used in the management of inflammatory arthritis may impair the effectiveness of ICI. However, albeit limited data, there has been no evidence to suggest that immunosuppressive treatment dampen the effectiveness of ICI[31,32].

Sicca syndrome and other ocular diseases

Xerostomia and keratoconjunctivitis sicca that resemble Sjogren's syndrome have been reported in patients treated with ICI[18]. They usually occur abruptly within the first three months of treatment. Xerostomia usually predominates while parotid swelling and parotitis occurs rarely. Most patients are seronegative for autoantibodies to Ro/SSA and La/SSB[33].

ICI has also been associated with other forms of ocular inflammation like uveitis and peripheral ulcerative keratitis[34]. Salivary gland biopsies show a varied histopathologic findings ranging from histopathology finding similar to Sjogren syndrome to diffuse T cell lymphocytic infiltration with acinar injury[33].

Management

Management of ICI induced sicca syndrome is similar to that of primary Sjogren's syndrome. Dental care with saliva substitutes and sialagogues is important in patients with xerostomia. Parotid gland swelling and/or parotitis is usually managed by giving prednisone (10mg – 40mg) tapered off over weeks.

The treatment of severe oral adverse effects involves discontinuation or temporarily withholding ICI, use of moderate to high doses of prednisone, diet restriction to purees and use of oral lubricants. The patient should also be referred to an oral medicine specialist. ICI can be reinitiated after at least three months following successful glucocorticoid taper[33].

Artificial tears should be prescribed to patients with ICI associated dry eyes. Furthermore, the patients should avoid other medications that cause dryness of the eyes. Patients with severe or refractory symptoms should be referred to an ophthalmologist.

Polymyalgia rheumatica/giant cell (temporal) arteritis

Clinical features and diagnosis

Polymyalgia Rheumatica (PMR) and Giant Cell Arteritis (GCA) are rare rheumatological irAE. They can occur in isolation or in combination. The median time of onset is three months after initiation of ICI. Similarly, to non-ICI PMR and/or GCA, the patients are elderly with a median age of about 57 years[35,36]. The clinical presentation of PMR is similar to those patients who have not received ICI.

A prompt temporal artery biopsy should be done to confirm the diagnosis in patients in whom GCA is suspected. The biopsy finding is similar to non-ICI GCA. Surrogate inflammatory markers like C-Reactive Protein(CRP) and Erythrocyte Sedimentation Rate (ESR) may be elevated due to malignancy and may not be useful for diagnosis. However, if CRP and ESR are normal, then GCA is very unlikely.

The role of imaging has not been well characterized. However, an ultrasound or MRI may be useful to support a PMR diagnosis if bursitis or tendinitis is seen in the classic areas and in patients who have PMR like symptoms with normal levels of inflammatory markers.

Treatment

The treatment for GCA and PMR is similar to that in patients without ICI therapy. Glucocorticoids are the mainstay of treatment. Higher doses of glucocorticoids may be required in GCA than with PMR[14]. The higher

doses of glucocorticoids used for the treatment of GCA requires withholding or discontinuation of ICI, while in PMR, due to the lower doses used, ICI may not be discontinued. The role of biologic agents like tocilizumab is unclear[36].

Inflammatory myopathies

Dermatomyositis and polymyositis are uncommon irAEs of ICI therapy[11,37]. Most patients present with proximal myopathy, similar to the classic form of the disease, but there have been a few reported cases of respiratory muscle and facial muscle involvement[38,39]. In addition, some patients may have concomitant myasthenia gravis and/or myocarditis[40,41].

The diagnosis is based on physical examination and elevated muscle enzymes supplemented by either an electromyography or muscle MRI. The role of muscle biopsy is unclear because of different histopathological patterns[11,39,42].

Glucocorticoids are the mainstay of treatment ranging from 30mg prednisone daily to 1000mg methylprednisolone. This is followed by gradual dose tapering[11,37]. Intravenous Immune Globulin (IVIG) can be used in patients with severe myopathy, respiratory distress and/or concomitant myasthenia gravis[43]. ICI should be discontinued in all cases and it is unclear whether the patients can be safely rechallenged with ICI.

Other rheumatologic irAEs

These irAEs occur infrequently and literature review contains mostly of case reports and/or series. They include Antineutrophil Cytoplasmic Antibody (ANCA) associated vasculitis[44], eosinophilic fasciitis[13], systemic sclerosis[15], digital ischemia[45], and single organ vasculitis[12,46]. The optimum treatment approaches have not been determined for these irAEs, and the treatment recommendations for the classic forms should be followed. The treatment options should be discussed in collaboration with the rheumatologist, oncologist and the patient.

It is important to note, that there may be other unreported rheumatologic irAEs. Hence a careful history of cancer therapies should be taken for patients presenting with rheumatological symptoms and history of cancer.

Pre-existing rheumatological diseases

There is limited data on the efficacy and safety of ICI therapy in patients with pre-existing rheumatological diseases as these patients have been excluded from clinical trials evaluating immunotherapy due to concerns about exacerbation of underlying disease and/or irAE[47]. However, some observational studies suggest that most of these patients can safely receive ICI[17,48]. About a third of patients with pre-existing rheumatological disease have experienced flares when started on ICI treatment[49]. Most of these have been successfully managed with the use of glucocorticoids but some have required discontinuation of the ICI therapy[50]. Severe flares may require treatment with other biologic agents like TNF inhibitors.

Patients with established rheumatological diseases who are on ICI therapy should be closely monitored by their rheumatologist and oncologist. The effect of DMARDs on immunotherapy is unclear, however hydroxychloroquine, sulfasalazine and low dose glucocorticoids can be safely used concurrently with ICI.

Conclusions

A spectrum of rheumatological irAEs can occur as a result ICI treatment. The most common being inflammatory arthritis. The precise epidemiology is not known. Several factors, namely the severity of irAE, tumour response, relative risk and benefits of both rheumatologic and oncologic treatment options and patients' preference, should be considered before determining the management approach. Most rheumatological irAEs can be managed successfully by use of glucocorticoids, the dose and duration depending on the severity of the irAE. Severe irAE may require temporary withholding or discontinuation of ICI and use of other biological agents like TNF inhibitors. Patients with preexisting rheumatological disease can safely use ICI albeit a risk of disease flare up.

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Malignancy and rheumatic disorders: a review

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Abstract

Background: Some malignancies may present or be associated with musculoskeletal manifestations. Additionally, therapies for malignancies can cause rheumatic disease syndromes.

Objective: The aim of this literature review is to address the various malignancies and their pharmacologic therapy that are associated with an increased risk of rheumatic disease.

Data source: The literature review uses medical science-based literature published locally and internationally on the risk of rheumatological diseases in patients with malignancies and the use of cancer chemotherapeutic agents.

Conclusion: Malignancies have been associated with a number of rheumatic manifestations either of the illness itself or as paraneoplastic syndromes. Similarly various rheumatological diseases may occur as a result of treatment.

Key words: Rheumatic diseases, Cancer, Chemotherapy, Immune-therapy, Malignancy, Screening

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Introduction

There is a bidirectional relationship between rheumatological diseases and cancer. Certain rheumatic disorders and their treatment may increase the risk of malignancy. Conversely, some malignancies may present or be associated with musculoskeletal manifestations. Additionally, therapies for malignancies can cause rheumatic disease syndromes[1,2]. The rheumatic presentation of malignant disorders and rheumatic symptoms caused by anti-tumour therapies will be reviewed here.

Malignant diseases with musculo-skeletal manifestations

A variety of malignancies can have musculoskeletal manifestations[3]. The most common manifestation is bone pain that occurs more frequently with in patients with bone metastasis and multiple myeloma.

The articular and systemic autoimmune phenomena occur not only as paraneoplastic rheumatologic syndromes but also as a direct consequence of some malignancies like lymphoproliferative and myelodysplastic disorders. About 25% of patients who had been admitted to hospital with rheumatological disease had occult malignancy[4]. The rheumatic symptoms usually improve on tumour remission.

Lymphoma

Articular symptoms in lymphoma may result from hyperuricemia that manifests as secondary gout due to increased cell turnover. It can also occur due to infiltration of the synovium by abnormal lymphomatous cells[5]. However, joint infiltration by lymphomatous cells is unusual and tends to occur primarily with T cell lymphomas. Synovial fluid analysis shows atypical lymphocytes while synovium biopsy will show infiltration by lymphoma cells[6].

In addition, some clinical features of lymphomas may mimic systemic inflammatory and autoimmune rheumatic disorders. For example, patients with angioimmunoblastic T cell lymphoma present with arthritis, skin rash, Coombs-positive haemolyticanaemia, fever and weight loss which may be suggestive of systemic lupus erythematosus or Still's disease. Similarly, patients with predominantly extra nodal lymphoma may be confused to be having granulomatosis with polyangiitis or lymphomatoid granulomatosis.

Large granular lymphocyte syndrome

Large granular lymphocyte syndrome is a chronic lymphoproliferative disease characterised by lymphocytosis, bone marrow infiltration, splenomegaly, neutropenia and anaemia. Thirty percent of the patients also have Rheumatoid Arthritis[7]. This could also fulfil the clinical criteria for Felty syndrome. Furthermore,

due to the clonal lymphocyte expansion, large granular lymphocyte syndrome can lead to development of eosinophilic fasciitis[8].

Leukaemia

Four percent of adults and 14% of children with leukaemia will present with either symmetrical or migratory polyarthritis[9,10]. Acute lymphoblastic leukaemia is the predominant leukaemia causing arthritis in children, while in adults it is acute lymphoblastic leukaemia, acute myeloid leukaemia and chronic lymphocytic leukaemia.

The pain in leukaemic arthritis is severe and unresponsive to antirheumatic medications[11]. Radiographs reveal more osteopenia and earlier lytic lesions than one would expect.

The joint manifestations in leukaemia are due to synovial infiltration by leukemic cells, hemarthrosis and periosteal or capsular lesions. Synovial biopsy may be diagnostic but due to the patchy nature of neoplastic involvement, it can be negative. This can be complemented by immunocytologic analysis of the synovial fluid. Leukemic synovitis is a sign of aggressive disease and should prompt immediate leukaemia directed therapy[12].

Myelodysplasia

About a quarter of patients with myelodysplasia have autoimmune abnormalities[13]. The most common manifestation is polyarthritis that mimics rheumatoid arthritis. Most of the patients are seronegative for Rheumatoid Factor (RF) and anti-citrullinated peptide antibody, neither do they show joint erosion on radiography. The arthritis precedes the diagnosis of myelodysplasia in about 50% of the cases. Myelodysplasia should be suspected if there is persistent cytopenia and raised acute phase reactants despite adequate control of the arthritis[14,15].

Rheumatic disorders associated with treatments for malignant disease

There are a number of rheumatological disorders that may arise because of treatment, especially with chemotherapy. These disorders are referred to as post chemotherapy rheumatism or chemotherapy related arthropathy[16,17]. Furthermore, there are concerns that radiation therapy may also increase the risk of rheumatologic diseases and with rheumatologic diseases have higher risk of getting radiation toxicity. Additionally, cancer immunotherapies, especially immune checkpoint inhibitors have been associated to a number of rheumatic and musculoskeletal disorders. These will be further discussed below.

Chemotherapy related musculoskeletal disorder

Aromatase Inhibitors

Aromatase Inhibitors (AIs) are used in the treatment of hormone receptor positive breast cancer. The drugs in this class include letrozole, anastrozole and exemestane. They suppress plasma oestrogen levels by inhibiting aromatase. Aromatase is an enzyme that is responsible for the peripheral conversion of androgens to oestrogens.

AIs are associated with a constellation of musculoskeletal symptoms ranging from arthralgia, joint stiffness, bone pain to Carpal tunnel syndrome. These constellations of symptoms are collectively known as AI associated musculoskeletal syndrome (AIMSS)[18-22]. AIMSS occurs in up to 50% of the patients and are severe in a third of the patients[20]. This leads to discontinuation of treatment in 15 – 20% of the patients[19-22].

The aetiology of AIMSS is not known but decreased oestrogen levels may play a role[21-24]. Furthermore, about half of the women who develop AIMSS have pre-existing musculoskeletal disorder[22].

The following strategies may aid in management of AIMSS

1. *Exercise and Nonsteroidal Anti-inflammatory Drugs (NSAIDs):* The initial strategy for managing AIMSS includes exercise and NSAIDS. In the HOPE trial, 121 postmenopausal women with AI associated arthralgias were randomly assigned to an exercise regimen or to usual care[25]. The patients in the exercise regimen had reduction in both their worst pain score (20% versus 1%) and pain severity (21% versus 0%) compared with usual care. A greater reduction in worst pain score (25% versus 14%) was noted in those patients who attended more than 80% of the exercise session. In addition, the primary treatment of AIMSS often begins with administration of NSAIDs, as they constitute mainstay treatment of pain.
2. *Temporary discontinuation of AI, followed by initiation of a different AI:* For women, in whom conservative measures including exercise and NSAIDs have been unsuccessful, we can discontinue treatment for two to eight weeks and then re-initiate with a different AI[26].
3. *Duloxetine:* Duloxetine is the next option if symptoms persist despite the above measures. In the SWOG S1202 trial, those patients randomised to duloxetine experienced improvement in joint pain relative to placebo[27].
4. *Acupuncture:* This is a non-pharmacologic method used in the management of AIMSS. Although the benefits are not so large, we consider as an appropriate

option for those patients who have been unsuccessful with the above steps or for those who cannot tolerate duloxetine[28].

5. *Switch to tamoxifen:* Tamoxifen is a Selective Oestrogen Receptor Modulator (SERM). It inhibits growth of breast cancer cells by competitive antagonism at the oestrogen receptor. Although AIs have a modestly better outcome than tamoxifen, some women may tolerate the toxicities of tamoxifen better than the toxicities of AI.

Bleomycin

Bleomycin has been associated with systemic sclerosis. It was noted to induce skin and lung fibrosis in animal models[29]. Similarly, there have been several cases of systemic sclerosis with Raynaud's phenomenon in patients undergoing treatment with bleomycin[30]. It is postulated that bleomycin causes chromosomal breaks by oxidation that leads to formation and release of autoantigens that leads to development of systemic sclerosis[31].

Taxanes

In addition to causing arthralgia and myalgia in about 60% of patients, taxanes cause Subacute Cutaneous Lupus Erythematosus (SCLE). SCLE is manifested by annular or polycyclic, photo distributed erythematous, and scaling lesions. Both phototoxicity and autoimmunity play a role in the pathogenesis as evidenced by presence of immunoglobulin G deposits in the keratinocytes and presence of anti-Ro/SSA antibodies[32].

Gemcitabine

There have been a couple of case reports that associate gemcitabine with causing systemic sclerosis with Raynaud phenomenon. The first case report is of a patient who was undergoing treatment of metastatic urothelial carcinoma of the bladder with gemcitabine, she developed scleroderma like changes after two cycles of gemcitabine. Cutaneous biopsy revealed diffuse sclerosis. Discontinuation of gemcitabine lead to partial reversibility of the fibrotic features[33]. The second case is of a woman with scleroderma who developed multiple ischemic digits after chemotherapywith gemcitabine[34].

Radiation therapy

External neck irradiation may lead to radiation induced hypothyroidism. This can manifest as myalgia, joint stiffness and elevated creatine kinase. The effect is dose dependent with a gradual onset with many patients having subclinical hypothyroidism for several years before developing overt disease[35-36].

Xerostomia, may mimic the dry mouth of Sjogren's syndrome. Similarly, radiation therapy may trigger morphoea (localized scleroderma).

Safety of radiation therapy in patients with rheumatologic disease

Several studies have suggested that patients with systemic sclerosis and systemic lupus erythematosus are at a greater risk of radiation toxicity[37-38]. However, a 2006 systematic review found methodologic shortcomings in most studies and failed to demonstrate that patients with rheumatologic diseases are at a greater risk of radiation related toxicity. Hence, radiation therapy is not contraindicated in patients with rheumatologic disease[39].

Immune Checkpoint Inhibitor

Immune Checkpoint Inhibitors (ICI) are a type of cancer immunotherapy that work by blocking the negative regulation of T cells. They block inhibitory molecules on T cells, antigen presenting cells and tumours, thus allowing an enhanced endogenous T cell mediated immune response to cancer. Their effectiveness was first demonstrated in malignant melanoma in 2011 and since then they have been approved in management of various types of malignancies. Despite their important clinical benefits, ICIs are associated with a unique spectrum of adverse effects that are collectively termed as immune-related adverse events (irAEs). The irAEs occurs due to immune activation and increased inflammation by these drugs and can affect nearly every organ system[40]. The rheumatologic adverse effects include myositis, inflammatory arthritis, sicca syndrome and vasculitis[41]. Temporary immunosuppression with glucocorticoids or other immunosuppressive drugs like tumour necrosis factor-alpha antagonist and mycophenolate mofetil can be effective in management of most cases of irAEs[42]. The rheumatologic complications of ICI and their management will be discussed in detail separately.

Conclusions

Malignancies have been associated with a number of rheumatic manifestations either of the illness itself or as paraneoplastic syndromes. Similarly various rheumatological diseases may occur as a result of treatment.

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Asymptomatic hyperuricemia: which patient should be treated?: a review

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Abstract

Background: Patients with Asymptomatic Hyperuricemia (AHU) are often unnecessarily and almost systematically treated with Urate-Lowering Therapy (ULT), risking severe and sometimes fatal adverse effects. While symptomatic HU is almost always easily diagnosed and treated, ULT in AHU remains controversial. We performed a literature review to determine which patient should be treated, in light of the lack of consensus guideline. In fact, recommendations are still controversial regarding indications of ULT in asymptomatic hyperuricemia patients. Relevant databases were searched, and eligible trials were assessed.
Objective: The aim of this review was to present data on when ULT treatment should be initiated.
Data source: A literature search in Pub Med.
Results: Current research remains controversial. While non-pharmacological therapy with diet restriction and exercise is recommended for all patients with AHU, further studies identifying guideline for the ULT for AHU would be beneficial. However, some practical key points are to consider: ULT is not likely to slow Chronic Kidney Disease (CKD). Consequently, patients with better preserved renal function and children, might benefit more from an early ULT. However, more studies are needed to investigate if ULT decelerates GFR decline and progression to CKD (especially Stages III-V) and if patients with CKD benefit from ULT. Maintain lifelong serum uric acid levels lower than 6mg/dL for patients at high cardiovascular risk and the target level should be 5mg/dL. Allopurinol is recommended as a first-line ULT. To this end, we propose a practical algorithm for the management of AHU and hope that our work will be useful in making therapeutic decision.

Key words: Asymptomatic hyperuricemia, Crystals depositions, Joint ultrasound, Comorbidities, Therapeutic approach, Allopurinol

Introduction

Uric acid is a weak organic acid, the end product of purine nucleotides degradation[1]. It is known as the major antioxidant agent in human plasma. However, its antioxidant nature comes to its own opposite within the cell, where it paradoxically converts to a pro-oxidant agent, which mostly targets lipids (LDL and membranes)[2]. Its concentration is controlled by synthesis and cell turnover and, on the other hand, by the rate of destruction, excretion, and reabsorption by the kidney[3]. Hyperuricemia is a common metabolic disorder. It occurs when inherited or acquired conditions decrease the ability of the kidneys to secrete uric acid, since more than 70% is excreted by the kidneys[4]. It has a male dominance. In women, the incidence increases in postmeopause. It can be diagnosed by the level of Serum Uric Acid (SUA) above 420µM (70µg/ml). AHU is defined as an abnormally high serum urate level, without gouty arthritis or nephrolithiasis[5]. It leads to widespread uric acid deposition in a variety of tissues. The first clinical presentation of hyperuricemia is the development of gouty arthritis. If left untreated, crystal deposition can occur in multiple joints, and generate a significant inflammatory response[6]. On the other hand, experimental studies show that MSU crystals can also deposit in blood vessel walls, which could lead to many cardiovascular diseases such as arterial hypertension, stroke, and heart diseases[7,8], and in the kidneys, resulting in a chronic kidney disease[9]. If the clinical significance of hyperuricemia as a risk factor for vascular events remains unresolved, this will lead to ambiguity regarding the need to treat asymptomatic hyperuricemia[10,11]. For the rheumatologist, the use of ultrasound to detect early crystal deposits on joints in subjects with asymptomatic hyperuricemia may help to make a good therapeutic decision in a complex situation.

Materials and methods

In this narrative review, we performed a literature search in PubMed on articles published in English between January 2001 and September 2021, using the term " asymptomatic hyperuricemia treatment" in combination with (AND) "chronic kidney disease", "metabolic syndrome", "cardiovascular disease", and "ultrasonography". In addition, we searched websites of guideline-producing organizations, including the American College of Rheumatology and the Japanese Society of Gout and Nucleic Acid Metabolism. More than 400 articles were found, and we chose the most relevant ones according to their titles. Articles relevant to these searches were also identified in the authors' personal files.

Results

Asymptomatic hyperuricemia (AHU) is a very common condition in daily practice, evaluated by different specialties, mainly nephrology, cardiology, and rheumatology. We will respectively review the viewpoints of these specialties, then we will suggest a practical algorithm for the management of AHU and hope that our work will be useful in making therapeutic decisions. We identified a total of 435 articles. These articles were reviewed for relevance to the topic. A total of 27 studies were included in this review, among which 10 meta-analysis, 5 societies' guidelines and recommendations, and 2 systematic reviews. We focused on articles on the management of AHU and excluded articles on symptomatic hyperuricemia. In Africa, the lack of local guidelines due to the scarcity of epidemiological and therapeutic data make it difficult to make recommendations on gout or the management of hyperuricemia with specific regard to the African continent. More detailed information on gout in Africa could be found in a study by Genga *et al*[12] and other studies[13-16].

Hyperuricemia and renal diseases

It is now well established and there is increasing evidence, based on both experimental and epidemiological findings, that hyperuricemia represents a risk factor for the development and progression of CKD[17-23]. The relationship between hyperuricemia (HU) and chronic kidney damage is bidirectional. Although a reduction in Glomerular Filtration Rate (GFR) can precede and lead to the development of hyperuricemia, increased SUA levels can negatively impact renal function[24–25]. Several epidemiological studies suggest that elevated uric acid is strongly associated with the development of CKD but not universally with the progression of CKD. In a recent meta-analysis involving 13 observational trials with more than 190,000 patients with normal renal function, the presence of hyperuricemia was an independent predictor of the development of CKD. In hyperuricemia, the risk of new-onset CKD was twofold increased, and this effect was seen with comparable magnitude in both patients with and without diabetes[26]. These findings establish a firm association between hyperuricemia and the development of nephropathy in healthy subjects. However, evidence for secondary prophylaxis (i.e., prophylaxis for progression) in patients with CKD still remains debatable. Certain epidemiological studies showed no relationship between hyperuricemia and the progression of kidney disease[27,28]. Whether ULT retards the progression of CKD is still seriously controversial. While previous small-controlled clinical studies suggested a positive effect[29], recent trials on the role of allopurinol in preventing CKD progression did not confirm any favourable effect. Two large, randomized-controlled clinical trials, recently published in the *New England Journal of Medicine*, confirmed these findings. The PERL trial (Preventing Early Renal Loss in Diabetes) looked at the effect of allopurinol on preventing glomerular filtration decline in type 1 diabetes patients with mild to moderate diabetic nephropathy[30]. The CKD-FIX trial, which included both diabetic and non-diabetic patients, evaluated the effect of the inhibition of xanthine oxidase on the progression of kidney disease in patients with CKD, a lower baseline glomerular filtration rate, and a high risk of progression[31]. Both studies did not confirm a favourable effect of allopurinol on the evolution of kidney disease, but they had several limitations. Chen Qi *et al*[32] found that ULT was associated with the reduction of blood pressure and retardation of the decline in GFR overtime. The authors did not find benefits in clinical outcomes, including major adverse CV events, all-cause mortality, and kidney failure, but results were conditioned by short follow-up or low quality of the trials[32]. In summary, the nephroprotective role of ULT is still not confirmed; further trials may demonstrate its beneficial effect. Moreover, ULT is not likely to slow CKD. Therefore, patients with better preserved renal function and children might benefit more from an early ULT.

Hyperuricemia and cardiovascular diseases

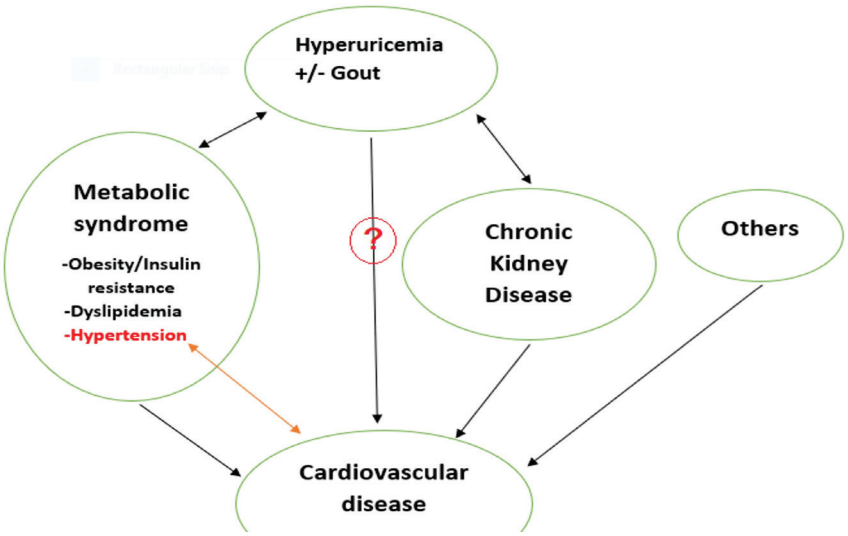
Over the last 20 years, the association of hyperuricemia with cardiovascular diseases has been re-examined following the demonstration in animal models that hyperuricemia could cause vascular disease[33-35]. Aside from its known antioxidant effect, strictly extracellular, soluble intracellular uric acid appears to cause significant endothelial and vascular disorders. Several mechanisms were suggested to explain its role, such as activation of the renin-angiotensin system, stimulation of smooth muscle cell proliferation, reduced nitric oxide synthase activity, and increased insulin resistance[36]. Furthermore, more recent evidence suggests that HU is linked to arterial obstruction by increasing plaque fragility in connection to hyperlipidaemia and decreasing fibrous volume[37,38]. In one study on coronary arteries obtained from 55 explanted hearts, monosodium urate crystal deposition was found in 6 cases[39], suggesting their role in the high rate of cardiovascular death[40], coronary heart disease[41],

heart failure, atrial fibrillation[42], stroke[43], and leading to refractory hypertension. Some authors suggest a role also for xanthine oxidase, which is responsible for oxidative processes[44], that themselves have an independent effect on CVD by endothelial dysfunction. Thus, in the case of xanthine oxidase inhibitor treatment, allopurinol improves endothelial function by profoundly reducing vascular oxidative stress and not by lowering UA[44]. Aside from this potential causal relationship between SUA and CVD, other authors[45], have reported a link between hyperuricemia and some known cardiovascular risk factors[45]. We look forward to the results of the ALL-HEART study, which is an ongoing multicentre, controlled, prospective, randomized trial examining the effects of allopurinol (up to 600mg daily) vs. no treatment on cardiovascular outcomes in patients with coronary artery disease. The secondary goals are to determine the cost-effectiveness of adding allopurinol to usual therapy, whether allopurinol improves quality of life, and to determine the safety and tolerability of giving allopurinol to patients with ischemic heart disease (without a history of gout)[46]. Several studies have confirmed the relationship between SUA and CVD mortality[47,48]. However, in their analysis, Rahimi-Sakak *et al*[48], found that the association between SUA level and CVD mortality risk, although positive in pooled results (HR 1.45, 95% CI 1.33–1.58, I2 = 79%), was stronger in women than in men. In addition, there was a significant non-linear association between them (r = 0.0709, p = 0.001). The Japanese Guideline on the Management of Asymptomatic Hyperuricemia (JGMHG), 3rd edition recommends pharmacological treatment of hyperuricemia in patients with CKD, emphasizing the importance of the cardio-renal continuum for treatment of asymptomatic hyperuricemia patients with hypertension and heart failure[49]. Recently, an updated management strategy with five-step recommendations for the treatment of 140 patients with increased SUA levels has been developed as illustrated in Figure 1. Finally, the definite answer to the difficult problems of independence of UA in relation to cardiovascular risk, especially the causality and reversibility issues, could not be obtained without a positive therapeutic trial. Cooperation between cardiologists, nephrologists, and rheumatologists is crucial in ULT trials.

Rheumatology's viewpoint on AHU: Gout is a systemic disease that results from the deposition of MSU in tissues. The clinical picture of gout includes asymptomatic hyperuricemia, acute gouty arthritis, the inter-crisis period, and chronic tophaceous gout[50]. The gold standard for its diagnosis is the visualization by optic microscopy of crystals in synovial fluid[51-53]. One study found that almost 10% of adults are documented to have hyperuricemia at least once in their lifetime, but only 22% of people with extremely high levels of SUA (more than 535mol/L, e.g., 8,9 mg/dL) will develop symptomatic gout during the five-year period of follow-up[54].

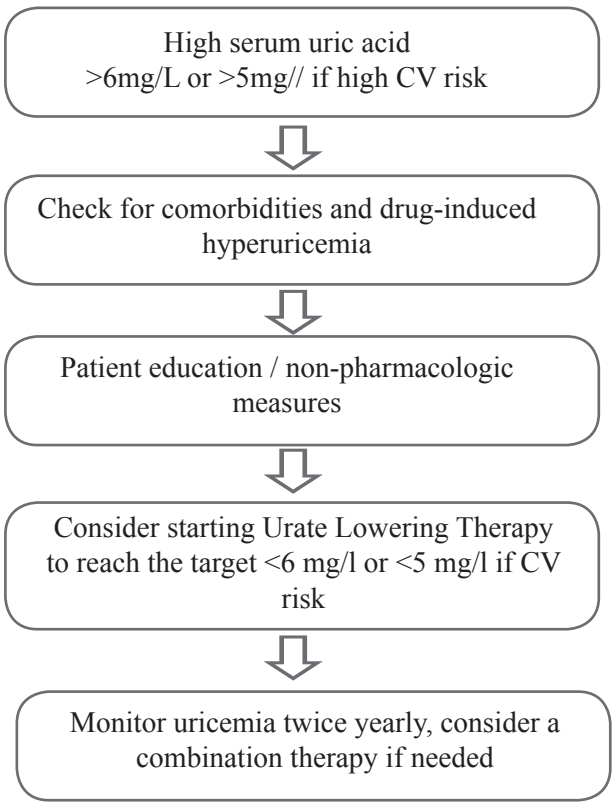
A prediction tool for incident gout among those with hyperuricemia: Siemons *et al*[54] developed an easy-to-use prediction tool for identifying patients with asymptomatic hyperuricemia at high risk for developing gout. The tool was developed using the risk factors of known gout, such as high blood pressure, diabetes, kidney failure, diuretics, obesity, and alcohol consumption, but also other factors such as age, gender, ethnicity, anaemia, blood lead, etc. The resulting simplified prediction tool (Figure 2) discriminated well between patients from different risk strata. If the score is 8 or less, the risk of gout is low. If it is 18 or more, the risk is high. If low-risk patients are considered to be the reference, the risk of incidental gout is 1.77 (CI95: 1.57–1.99) and 3.75 (CI95: 3.13–4.48) for patients at moderate and high risk, respectively. The odds ratios of prevalent gout are 3.37 (95% CI: 2.17–5.20) and 4.38 (CI95: 1.50–24.93) for patients at moderate and high risk, respectively. This easy-to-use score may allow us to assess the risk of gout in a population with hyperuricemia. It's stays to be validated prospectively

Figure 1: Illustrates the relationship between recognized CV risk variables and hyperuricemia, highlighting the challenges in establishing a direct causal link between hyperuricemia and CVD. (Shah, 2017)



in asymptomatic populations, where it will have its full place if its metrological properties are confirmed.

Figure 2: Illustrates a s-step strategy for the management of hyperuricemia; CV -cardiovascular (Borghi, *et al.* 2021[15])



Association of three genetic loci with uric acid concentration and risk of gout: Dehghan *et al*[55] identified three genetic loci (SLC2A9, ABCG2, and SLC17A3). Gout is associated with uric acid concentration and gout. A score based upon genes with a putative role in renal urate handling showed a substantial risk for gout.

Ultrasonography's role in early gout diagnosis: Ultrasonography (US) might appear as a useful tool in the management of this disease. In gout, two US features are quite specific and might be pathognomonic: the double contour sign and aggregates evocative of tophus[56–59]; Furthermore, MSU crystal deposition can be seen in ultrasound (US) images not only in inflamed joints but also in joints that have never been affected by overt arthritis[60]. The sensitivity of the ultrasound urate tissue deposition finding (double contour sign or tophus) is variable and ranges from 20% to 90%, which depends on previous therapy, data availability, study type (prospective or retrospective), type of observed joints, etc. The specificity is 98-100%. The most acceptable balance of sensitivity and specificity was reached by Naredo *et al*[61]. US examination standard recommendation[61], which demands evaluation of 6 anatomic structures bilaterally and simultaneously (12 regions): 3 structures for Tophus hyperechoic aggregates: 1 joint-radiocarpal and 2 tendons-patellar ligament and the triceps muscle tendon and 3 cartilages for the double contour sign: first metatarsophalangeal joint, second metacarpophalangeal joint, and calcaneal or femoral condyle cartilage. The sensitivity of Naredo's examination is 85%, specificity 83%, positive predictive value 92%, and negative predictive value 71%[62]. In light of this data, we can consider that US might be a valuable tool to identify hyperuricemia patients at risk for gouty arthritis. Dual energy CT and MRI could be used for the detection of MSU crystal deposits and tophi. However, ultrasound remains the cheapest and most convenient tool.

In summary, if for gout management, strong recommendations have been generated by international specialty societies, it is still controversial for AHU individuals. Currently, there is still considerable disagreement with regard to whether AHU should be treated,[62–64], probably due to the fact that both low and high SUA levels are associated with a high all-cause and cause-specific mortality rate with a U-shaped relationship[65,66]. Furthermore, a very low SUA level has some adverse effects, such as paradoxical arterial hypertension and increased dementia risk.

Figure 3: scoring chart for determining a patient's risk for developing gout. The risk is rated as low, moderate or high. (Siemons, *et al,* 2012[54])

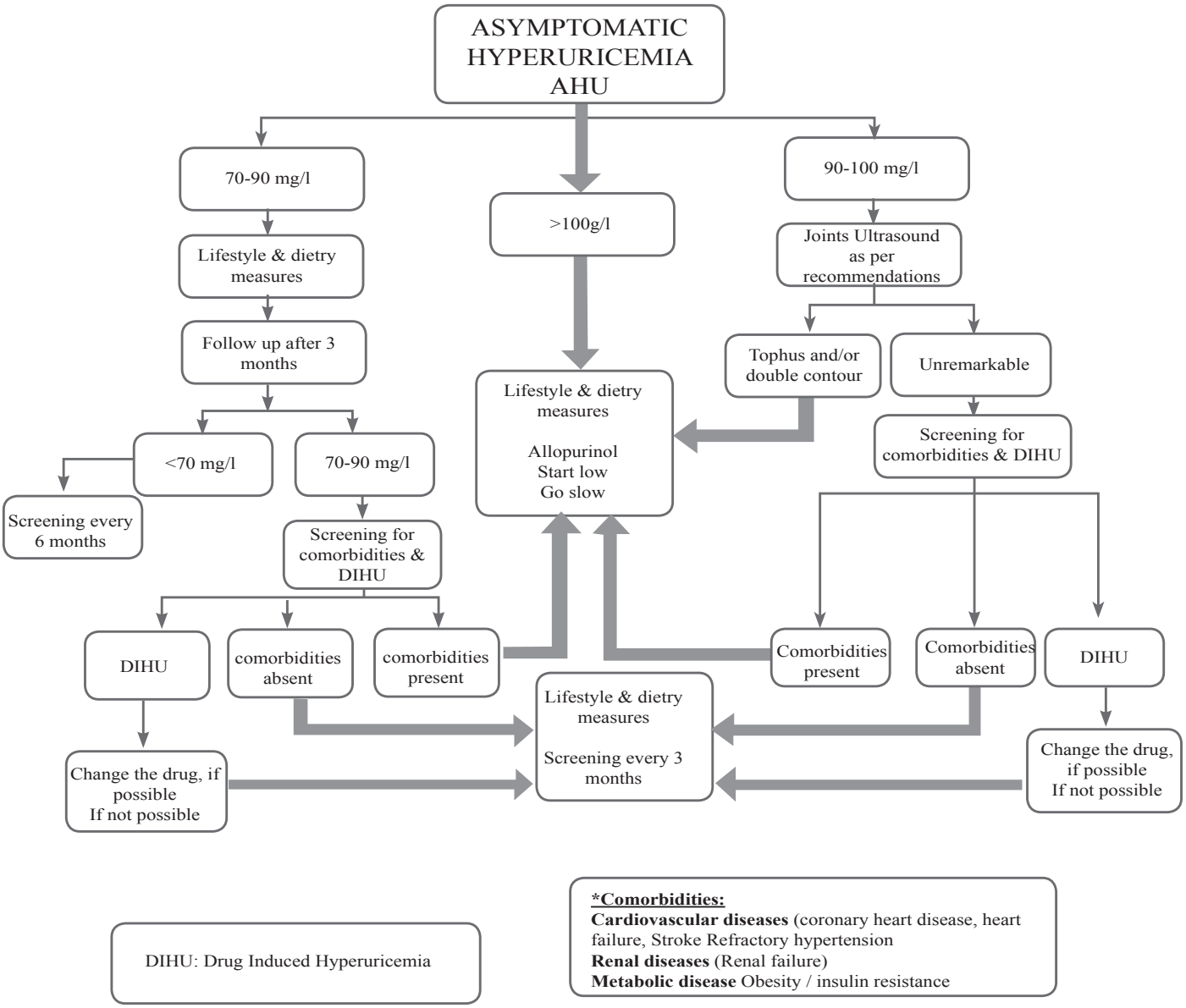
Patient's risk for gout
Start with a risk of 0

If:		Risk score
Age: < 45		+0
Age: 46-52		+1
Age: >53		+2
Body mass index: <25		+0
Body mass index: 25 - 29.99		+4
Body mass index: 30 - 34.99		+7
Body mass index: > 35		+9
Chronic kidney disease:	No	+0
Chronic kidney disease:		+2
Diabetes mellitus:	No	+0
Diabetes mellitus:	Yes	+3
Diuretic use:	No	+0
Diuretic use:	Yes	+6
Total score		0 - 25
If total score: 0 - 8		Low risk
If total score: 9 - 17		Moderate risk
If total score: 18 - 25		High risk

According to the American College of Rheumatology Guidelines 2020 for the Management of Gout, ULT is conditionally recommended even in patients with comorbidities and MSU crystal deposition as seen on imaging[67], which is consistent with Australian and New Zealand recommendations[68]. Conversely, the Japanese Guideline on the Management of Asymptomatic Hyperuricemia (JGMHG), 3rd edition, recommends pharmacological treatment of hyperuricemia in patients

with CKD, emphasizing the importance of the cardio-renal continuum for treatment of asymptomatic hyperuricemia patients with hypertension and heart failure. In order to reduce mortality in hyperuricemic patients with either hypertension or heart failure, ULAs could be used, when patients agree[68]. To sum up, given the lack of an international consensus on the management of AHU and based on the current data, we proposed an algorithm for the management of AHU taking into account uric acid level, joints ultrasound findings, and comorbidities (Figure 4).

Figure 4: Our proposed AHU therapeutic decision algorithm. Taking into account comorbidities, joints ultrasound findings, concomitant drugs, and SUA level



Conclusions

Current research on AHU management remains controversial. While non-pharmacological therapy with diet restriction and exercise is recommended for all patients with asymptomatic hyperuricemia, further studies identifying guidelines for the ULT in AHU would be beneficial. Patients with better preserved renal function and children might benefit more from an early ULT. However, more studies are needed to investigate if ULT decelerates GFR decline and progression to CKD (especially Stages III–V) and if patients with CKD benefit from ULT. Patients with comorbid CKD, CVD, urolithiasis, or hypertension, as well as those with asymptomatic hyperuricemia and MSU crystal deposition on imaging, which some authors consider to be pre-clinical gout, could be a candidate target group for prophylactic ULT, on which future research should focus. To this end, we proposed a practical algorithm for the management of AHU and hope that our work will be helpful in making therapeutic decisions. But our proposed algorithm should be evaluated in prospective studies.

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Difficult to treat rheumatoid arthritis: a review and relevance to Africa

Adelowo OO[1], Ekpenyong HJ[2]

Abstract

Background: Rheumatologists are sometimes confronted with rheumatoid arthritis patients, who despite adequate management are unable to achieve a remission or low disease activity; of recent, the terminology 'Difficult-to-Treat Rheumatoid Arthritis' has been adopted.
Objective: To identify the definition, causes, and management of these patients. The peculiar factors causing 'Difficult-to-Treat RA' in African patients are also identified.
Data source: These were obtained from literature search on this subject as stated in the references and on Pubmed search
Conclusions: Difficult-to-Treat RA constitutes a large group of patients in rheumatology practice. The causes are multifactorial. It is important to identify the factors responsible in the patients and institute appropriate measures. Since the definition factors the use of Biologics or JAK inhibitors, rheumatologists in Africa need to do further research on this subject while also providing the definition and management of this condition.

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Introduction

There have been a lot of development in the management of rheumatoid arthritis, beginning with numerous NSAIDs; glucocorticoids; early synthetic DMARDs such as D- penicillamine, Gold salts; newer synthetic DMARDs such as methotrexate, sulfasalazine, leflunomide, and hydroxychloroquine.

There are now numerous Biologic DMARDs which have revolutionized the management of RA. The latter have been followed very closely with the oral targeted therapy such as the Janus kinase inhibitors. At every stage of the evolution of these medications, the primary objective has been to achieve a remission and low disease activity, especially since a cure may be unachievable. There has also been evolution of various tools to measure in quantifiable numbers achievement of such remission with an option of low disease activity if the former is unachievable. The goals of remission and low disease activity are set up to minimize chronic pain, deformities, disabilities, other morbidities, and even deaths. Treatment to target enables us to set achievable goals. Despite all these medications, remission is not achievable in many patients and these have come to be classified in recent times as "Difficult-To-Treat Rheumatoid Arthritis" (D2T RA)[1] a nomenclature borrowed and adapted from similar concepts as used in medical specialties such as asthma, psychiatry and hypertension respectively[2-4]. When this term is used by rheumatologists, we are assuming that the patient is taking the medications as prescribed by a knowledgeable rheumatologist. We assume that the patient is not stopping the medications because of tolerability or affordability issues.

Definitions

Many attempts have been made to arrive at the definition of the term 'difficult-to-Treat RA'

The Task Force in charge of the 'Development of EULAR recommendations for the comprehensive management of difficult to treat rheumatoid arthritis' ruminated over this and had proposed different terms to describe this population, such as 'severe', 'refractory' 'resistant to multiple drugs or treatments' Eventually the term 'Difficult-to- treat RA' was chosen[1].

There are two major definitions:-

1. "Persistency of signs and/or symptoms suggestive of inflammatory RA disease activity despite prior treatment with csDMARDs and at least two bDMARDs" [5].
2. EULAR criteria which are fuller and more explanatory[1]. These criteria have been further expanded by van Laar at the 2022 Eular Congress as cited by Jason Liebowitz[6].

(i) Treatment according to EULAR recommendations of management of RA and failure of ≥ 2 biologic

DMARDs / targeted synthetic DMARDs (with different mechanisms of action) after failing csDMARD therapy.

(ii) Presence of at least one of the following: signs and/or symptoms suggestive of active or progressive disease. The latter is characterized by such features as moderate disease activity as assessed by Clinical Disease Activity Index (CDAI) or other tools; active synovitis on examination; elevated inflammatory markers; new erosive disease on imaging. Inability to taper glucocorticoid treatment to less than 7.5mg of prednisolone daily also qualifies as well as rapid radiographic progression. RA symptoms that are causing a reduction in quality of life are also factored as difficult to treat, as well as: -

(iii) The management of signs and/or symptoms is perceived as problematic by the rheumatologist and/or the patient.

The EULAR criteria for D2T RA were developed based on the data from a previous international survey; though this survey did not include African countries, as may be obvious in the emphasis on biologics, which are mostly unavailable or unaffordable. There are however some clarifications. For instance, a footnote on these set of criteria admits that 'socioeconomic factors may limit the access to expensive DMARDs (e.g., in low-income countries). As such a clause was added to the criteria to recognize this limitation. A previous study has identified lower socioeconomic status at onset of RA as an independent risk factor for the development of difficult-to-treat disease[7].

Why we should worry about "Difficult- to- treat RA patients"

High disease activity is normally associated with D2T RA thus leading to challenges with the following: - (a) social life (b) work ability (c) quality of life (d) psychological well-being (e) comorbidities (f) mortality (g) health care utilization, hospitals budgets and (h) society cost. All these will be particularly applicable to African countries. Studies have shown that "Difficult-to-treat" cases may be present in 5-20% of all patients with RA[1]

Factors contributing to "Difficult-To-Treat RA"

There are many factors, including delay in diagnosis, contributing to refractory or "difficult-to-treat RA"[8,9].

Determinants of drug loss of efficacy and "Difficult-to-treat RA"

1. Smoking[10]

a) Associated with immunologic mechanism in production of RF, ACPA.
b) Increased production of pro-inflammatory cytokines and T- cells with a resultant enhancement of systemic inflammation.
c) Smokers are shown to require higher doses of DMARDs, with the potentiality of resultant adverse effects.
d) However, studies (CORONA registry and BARFOT study) have not shown that cessation of smoking can influence disease activity[11].

2. Immunologic mechanisms[12,13]

a) The response to medications varies in patients because of the variable biology of underlying immunologic processes and pathways.
b) Variable synovial expression of TNF and presence of lymphocyte aggregates at the initiation of treatment with infliximab, for example, correlates with disease activity.
c) Variable treatment response to factors such as CD 68 positive macrophages and plasma cells.
d) Synovial fibroblast differences with resultant variable secretion of pro-inflammatory cytokines.
e) Different biomarkers reflecting exact molecular mechanism of inflammation are variable in individual patients.
f) It has also been shown that in patients with D2T RA, the persistent synovitis is regulated by stromal cell activities which are not affected by the medications used in the treatment of RA.

3. Pharmacogenetics[5]

a) This may explain the ineffectiveness of anti-rheumatic drugs and adverse drug reactions in patients. Different genetic make-up will result in variable responses and adverse effects.
b) For a drug like methotrexate, for example, folate antagonism also targets other related pathways – including homocysteine – methionine – polyamine pathway and purine metabolism. Thus, variants cause different effectiveness and toxicity.
c) Several polymorphisms of Anti TNF as seen in RA will result in variable responses.

4. Immunogenicity of biologic DMARD[14,15].

a) It is well known that 20-30% of RA patients may not respond to first bDMARD especially anti-TNFs
b) Within 2-3 years of initiating bDMARDs, 20% have secondary ineffectiveness.
c) Anti–drug antibodies (ADAs) play a big role, both neutralizing and non-neutralizing. This is more so with anti –TNFs, leading to loss of efficacy and adverse drug reactions (ADR),
d) Risk of ADAs is however reduced by 74% when there is concurrent administration of methotrexate.
e) Biologic DMARDs with low immunogenicity include rituximab, tocilizumab, and abatacept,

5. Recurrent drug reactions[5]

a) This can affect drug dosing, drug compliance, and subsequent treatment steps.
b) About 66% of all bDMARDs are discontinued over time due to adverse drug effects- 46% and loss of efficacy – 41%.

c) Increasing age increases adverse drug reactions.
d) High ESR, and CRP is associated with ADRs.
e) Patients generally report more ADRs than their physicians.
f) However, not all reported ADRs are due to the DMARDs as they may be due to other medications or co-morbidities.

6. Negative disease outcomes:

a) Over time, patients begin to doubt if they will ever get better. Psychological tiredness and frustration normally associated with chronic painful conditions.
b) Fibromyalgia and joint damage- frustration and negative disease outcomes as well as exaggeration of pain and adverse effects[16].
c) Secondary Sjogren's syndrome is associated with increasing pain.

7. Comorbidities

a) Obesity in particular can worsen the subjective measures of disease activity, reduce the likelihood of establishing remission, and can also reduce efficacy of drugs used. It may also reduce the probability of sustained remission.
b) ESR is higher in obese patients with tendency to over-treatment and adverse effects resulting in a vicious circle of pain, frustration, and poor drug compliance.
c) Certain medical comorbidities may cause DMARDs to be less effective. They can also facilitate adverse effects and may end up making it more difficult to grade the patient's disease severity and often leading to inappropriate treatment. An example is fibromyalgia which is commonly associated with RA.

8. Medication compliance

a) Compliance in rheumatic disease may vary between 30 - 99%.
b) Compliance in other chronic diseases generally may be up to 50%.
c) Multiple factors- the disease itself, adverse effects, pill overload, treatment characteristics (tablets, injections, infusions) characteristics of health care system – patients with HMO for instance do better than patients paying out of pocket.
d) Psychological state of a patient to the illness which may be one of optimism, pessimism, or nonchalance.
e) Associated psychological disorder – There is a well-recognized high prevalence of anxiety, depression, and alcohol use in patients with D2T RA.

9. Inappropriate medication responses

a) Poor drug storage. Electricity may not be available and as such biologics will lose their efficacy.
b) Poor communication with the rheumatologist or assistant.
c) Hearing difficulties, especially with elderly patients.

Peculiar factors contributing to "Difficult -To -Treat RA" in Africans

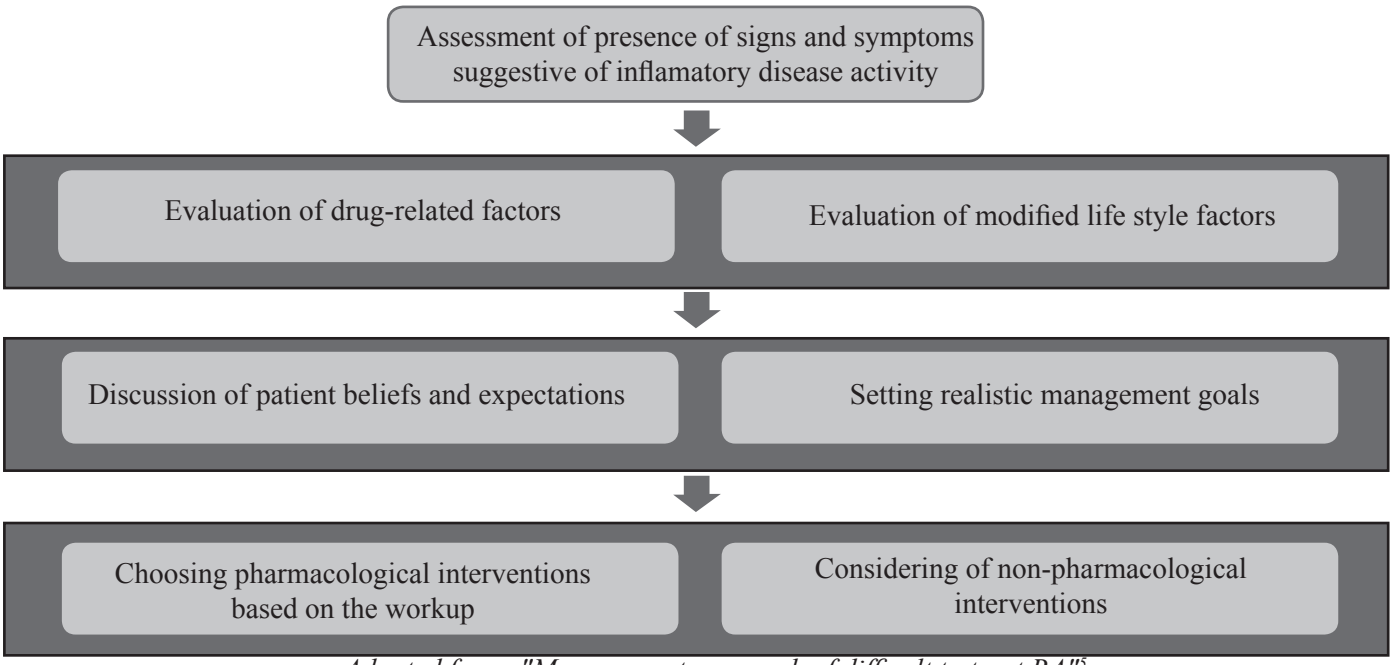
There are certain peculiar factors in African countries that may result in the inability of RA patients to achieve remission thus causing characterization as D2T RA.

i) Basic belief that RA is due to a 'Spiritual attack' or some evil spirits thus patient may stop taking DMARDs.
ii) Tendency to seek 'cheaper' treatment such as herbs because of the cost of DMARDs. We do not know what the drug-drug interaction will be in such cases.
iii) Poor education.
iv) Assumption that RA can be cured and thus patients tend to stop medications when pain appears less.
v) Ready availability of prednisolone over the counter. Patients indulge in them with attendant adverse effects and loss of drug efficacy.
vi) Lack of electricity and thus loss of efficacy of cold chain product as well as resultant possible adverse effects.
vii) Delay in presentation to a rheumatologist, averagely 3-4 years. Resultant high disease activity. Synthetic DMARDs may thus not work effectively.
viii) It is presently not possible for most African countries to apply 'Difficult-To-Treat' concept as enunciated by EULAR because of the non-availability or non-affordability of biologics and JAK inhibitors.

1. Education – Rheumatologists must work with, and on patients.
2. Psychological interventions such as cognitive behaviour therapy, mindfulness, relaxation techniques, hypnotherapy[2].
3. Physical therapy- Ultrasound, laser therapy, balneotherapy, electrotherapy, aerobic exercises, muscle strengthening, mobilisation, orthoses[2].
4. Special sports activities, dancing, tai-chi[2].
5. Diet.
6. Acupuncture.
7. Mimics of RA such as polyarticular gout and CDPD disease should be excluded.
8. Evaluation of drug related factors. Choosing a more appropriate bDMARDs for each patient based on the genomics.
9. Distinguish symptoms of ADRs from those caused by RA. May withhold medications for some time or lower the dose.
10. Factors such as non- compliance and inappropriate storage of bDMARDs to be identified.
11. Evaluation of modifiable lifestyle factors such as obesity, smoking cessation.
12. Setting realistic goals. Low disease activity if remission is not achievable.
13. Consideration of non-pharmacological interventions – Orthopaedic surgeon, pain physician, physiotherapy.
14. Careful choice of pharmacological agents.

Management

Figure 1: Schema showing outline of approach to management of "Difficult-To-Treat RA"



Adapted from; "Management approach of difficult to treat RA"[5]

Questions to ask ourselves as rheumatologists

1. Are we setting too high a target we want to achieve? Will moderate disease activity be sufficient in certain patients?
2. Will these patients do better when referred to another rheumatologist?
3. As more effective molecules are approved, will we still have difficult to treat RA in 10 years? Will our definition change?
4. Can African rheumatologists define their own 'Difficult to Treat' cases based on drugs available to them?
5. Can we change the order of our management? Can we for instance start with Biologics or JAK inhibitors?
6. Can we combine Biologics and JAK inhibitors?

Conclusions

The concept of "Difficult-to-Treat RA" is recent but it clearly identifies many cases of RA that do not reach target marks in diseases evaluation on treatment. The definitions based on poor response to Biologics and JAK inhibitors identifies that the patients are on optimal management regimens. Factors contributing to this poor response both globally and in African populations have been identified. It is important that African rheumatologists identify the factors contributing to "Difficult-To-Treat RA" and provide guidelines to its management taking into cognizance the poor penetration of Biologics and JAK inhibitors in most African countries.

Declaration: The article has been adapted from Janssen Virtual lecture "Rheumatology masterclass for sub-Saharan Africa: difficult to treat rheumatoid arthritis. What to do?" Adelowo OO. October 25, 2022

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Acalculous cholecystitis: A rare manifestation of acute abdomen in lupus

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Abstract

Lupus is an autoimmune disease of unknown aetiology with varied manifestations. There is a significant variation in the clinical presentation and severity of Gastro-intestinal (GI) disorders. The low index of suspicion often leads to delays in diagnosis and the wrong choice of management. Acute Acalculous Cholecystitis (AAC) is just one of the GI manifestations of lupus and is associated with high morbidity and mortality. There are few case reports of AAC in written literature. We introduce a 31-year-old black female who presented with abdominal pain that turned out to be ACC in a patient known to have lupus. She was successfully managed conservatively with steroids and antibiotics and did not require surgical intervention.

Key words: Systemic lupus erythematosus, Acute a calculous cholecystitis, corticosteroids, Kenya

Introduction

Acalculous cholecystitis is cholecystitis without evidence of gallstones or cystic duct obstruction[1]. It is usually associated with more severe morbidity and higher mortality rates than calculous cholecystitis[1]. There are several risk factors for developing AAC. Lupus accounts for 10% of cases of acute cholecystitis and is associated with high morbidity and mortality[2]. This partly may go unrecognized as a cause of abdominal pain. Abdominal pain in lupus can be a challenge due to the various possible aetiologies ranging from the disease to drugs used to treat the disease

Case report

A 30-year-old known lupus patient on hydroxychloroquine 200mg once a day and deflazacort 6mg referral from a peripheral facility with a three-day history of right upper quadrant pain, fever, and vomiting. This was associated with malaise, nausea, and poor appetite. She was diagnosed four years prior with lupus after presenting with fever, arthralgia, and symptoms of anaemia. At diagnosis, ANA and DsDNA were positive. On examination at admission, she had a body temperature of 38.5^{o}C, the pulse rate of 110/min, the respiration rate of 30/min, and the blood pressure of 130/90 mm Hg. She was pale and severely dehydrated. Physical examination revealed tenderness on the right upper quadrant of her abdomen and a positive Murphy's sign. Initial laboratory tests showed elevated ESR 50 mm/hr, CRP 222 mg/L, and WBC 13900mm^3. The haemoglobin and platelets were reduced by 8.5g/dL and 76,000/mm^3, respectively. The creatinine 109.2µmol/L and urea 7.7Mmol/l. the liver function tests had raised GGT and ALP at 355U/L and 150.3U/L, respectively, with a normal ALT and AST. The urinalysis had blood 1+, protein 1+. The complement levels were reduced with C3 at 70mg/dl and C4 at 5.22mg/dl. The chest X-ray was reported as normal. The CT scan abdomen demonstrated gallbladder wall thickening with pericholecystic edema without any evidence of stone or biliary sludge. Intravenous steroid pulse therapy (1g/day for three days) was done concurrently with ceftriaxone and metronidazole. The patient responded dramatically to treatment within 3-4 days. She did not undergo surgical intervention due to the excellent response to the steroids and antibiotics. She was discharged after ten days on steroid taper dose, hydroxychloroquine and azathioprine for review at the rheumatology and surgical clinic.

Discussion

The Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disease of unknown cause that presents as a multisystemic disease characterized by the presence of immunological abnormalities antibodies to nuclear and cytoplasmic[3]. This elaborate heterogeneous clinical presentation and pathogenesis of lupus can pose a diagnostic challenge for the

clinician. Several diagnostic criteria have been proposed from ACR 1997, then Systemic Lupus International Collaborating Clinics 2012 criteria and now 2019 EULAR/ACR classification criteria for SLE[4]. A score of >10 is diagnostic for lupus based on the 2019 EULAR/ACR classification criteria for SLE. A validation study on the three criteria revealed new criteria had an improved sensitivity of 96.1% and specificity of 93.4%, compared with 82.8% sensitivity and 93.4% specificity of the ACR 1997 and 96.7% sensitivity and 83.7% specificity of the Systemic Lupus International Collaborating Clinics 2012 criteria[4]. The prevalence of SLE varies by gender, race, and region. Its predominantly found in women with rates highest in black ladies then Asian and white race. Despite the highest rates in blacks, the paucity of data on the disease in Africa[5]. The diagnosis of lupus in Africa is still a challenge, mainly due to underdiagnosis. Reasons include the high prevalence of tropical diseases, low numbers of rheumatologists, low index of suspicion, inadequate infrastructure, and access to health[5]. Symptoms of lupus range from mild skin and joint presentations to severe life-threatening conditions such as renal and haematologic[3]. A review of lupus literature by Genga *et al*[5] revealed that the most common presentations in Africa were joint and skin.

Gastrointestinal manifestations are common in lupus, with up to 40% of patients experiencing them during their lifetime[6,7]. Examples include oral ulcers, lupus hepatitis, intestinal pseudo-obstruction, lupus enterocolitis, amongst others[6,7]. An acute abdomen usually poses diagnostic challenges in lupus. The potential causes of acute abdomen in lupus are spontaneous peritonitis pancreatitis and acalculous cholecystitis. Al-Hakeem *et al*[8] reported that 15% of patients with SLE presented with abdominal pain, which was attributed to cholecystitis in a review on 88 lupus patients done over 15 years. Acalculous cholecystitis accounts for 10% of all cases of acute cholecystitis and is characterized by necro-inflammatory pathogenesis affecting the gall bladder. It has multifactorial aetiologies, one of which is lupus and is associated with high morbidity and mortality. There are a few case reports of acalculous cholecystitis in the setting of lupus[9,10]. The pathogenesis of acalculous cholecystitis revolves around local inflammatory response that results from gallbladder stasis and ischemia[9-11]. In the setting of lupus, the cause is mainly attributed to vasculitis, thrombosis, or as part of an adverse reaction to the drugs used for treatment. Vasculitis can either directly affect the gall bladder or involve the mesenteric vein. When vasculitis directly affects the gall bladder, it leads to acute arteritis with periarterial fibrosis. Vasculitis can rarely cause mesenteric inflammatory veno-occlusive disease affecting mesenteric vein and its branches sparing the arterial vasculature[12]. The thrombotic disease is commonly observed in the background of antiphospholipid antibodies, presenting as thrombi in gall bladder veins with no evidence of vasculitis[12]. We suspect the patient had a vasculitis as clinical and radiology evaluations did not reveal evidence of thrombosis. Due to financial constraints, the antiphospholipid antibodies screening tests were not done.

Critically ill patients presenting with sepsis and acute abdomen diagnosis of a calculous cholecystitis should be suspected. Diagnostic evaluation should include haemograms, inflammatory markers, blood cultures, renal tests, liver tests, and pancreatic enzymes. Our patient had leukocytosis and elevated CRP suggestive of sepsis. Liver function tests suggested an obstructive picture that our patient had. Differentials include pneumonia and urosepsis. The urinalysis ruled out urosepsis, and a chest X-ray was reported as normal. Abdominal imaging includes either ultrasonography or contrast-enhanced abdominal Computed Tomography (CT) scan not only to the diagnosis of suspected acalculous cholecystitis but to rule out other potential causes of acute abdomen. Ultrasound findings have a sensitivity ranging from 30-92% with a specificity of 89 to 100%[13,14]. Sonographic Murphy's sign is indicative of gallbladder inflammation but very user-dependent. Gall bladder thickening has a high sensitivity but low specificity[13,14]. False positives mimicking gall bladder thickening include ascites, hypoalbuminemia gall bladder stones, and sludge. A significant limitation of ultrasonography is the ability to detect gall bladder abnormalities in a large number of critically ill patients, even in the absence of acalculous cholecystitis. One study recorded one ultrasonographic gall bladder abnormality in 84% and up to three abnormalities in 57% of the 44 patients recruited. The final tally of diagnosis of acalculouscholecystitis was two[15].

The precision of the CT scan appears to be comparable with ultrasonography[16]. The CT scan findings suggestive of acalculous cholecystitis include gall bladder wall thickening (>3mm), gallbladder distention (>5cm), subserosal edema, hyperdense bile (sludge), hyperdense bile (sludge), pericholecystic fluid, mucosal sloughing and intramural gas[17]. Of the above findings, those with the highest specificity include gas in the gall bladder wall, lack of gallbladder wall enhancement, and edema around the gallbladder at 99, 95, and 92%, respectively[17]. It is important to note that these findings have reduced sensitivity at 11, 38, and 22%, respectively. CT scan results should be interpreted with caution as critically ill patients have a high prevalence of gall bladder abnormalities: one case series noted the rate at 96%[17]. Clinicians should not use imaging alone to make the diagnosis due to the low sensitivity of most of the gall bladder abnormal findings. They should be interpreted in the context of the clinical presentation of the patient. Our patient's diagnosis was made based on symptoms of acute abdomen, sepsis, deranged liver function tests, and CT scan abdomen demonstrated gallbladder wall thickening with pericholecystic edema without any evidence of stone or biliary sludge.

The treatment for acute acalculous cholecystitis associated with lupus is controversial. Data on the

mortality rate of a calculous cholecystitis is at 30% but can go as high as 75% if treatment is delayed[17]. Traditionally early cholecystectomy was indicated in unselected AAC patients as they can rapidly progress to gall bladder necrosis, gangrene, and perforation, which are markers of poor prognosis[17]. However, new evidence shows that successful treatment outcomes are possible with a combination of corticosteroids, antibiotics, and supportive treatment[18,19]. Liu *et al*[19] compared treatment outcomes in 22 patients with lupus associated Acalculous Cholecystitis (ACC). They divided the patients into two treatment arms one with moxifloxacin alone and the other corticosteroid moxifloxacin combination. One patient in the combination arm had an inadequate response and had to undergo surgery. The moxifloxacin monotherapy arm had a higher failure rate; six of the ten had to accept cholecystectomy in the antibiotic group due to inadequate response[19]. During treatment, corticosteroids arm noted a reduction in the indexes of SLE activity such as SLICC/ ACR damage indexes, antinuclear antibody, anti-double stranded DNA antibody, and anticardiolipin antibody. They attributed the results to the pathogenesis of ACC in lupus being partly an inflammatory process with vasculitis; thus, the role of high-dose methylprednisolone as an anti-inflammatory[19]. Several case reports that have described successful outcomes of ACC with high dose steroids treatment[20,21]. Shin *et al*[20] recommended that if the patient's general condition is good, has no severe complications, has no other risk factors for ACC, and no evidence of infection, then one may consider high-dose steroid therapy as a first line of treatment. Based on the recommendations from Shin *et al*[20] as our patient met all of the criteria apart from evidence of infection together, we decided to start with high dose steroid treatment. Our patient also had markers suggesting high lupus activity, such as reduced complement, haemoglobin, and platelet levels. Our decision to combine with antibiotics was based on leukocytosis and results of the review by Liu *et al*[19]. The choice of antibiotic should be determined by the source of infection if its community-acquired versus healthcare-associated. Other factors that will determine the choice of antibiotics include bacterial cultures and the patient's risk factors for infection and possible risk of adverse outcomes[22]. Our empiric choice of ceftriaxone and metronidazole was based on the possibility that the source of the infection was community-acquired. Indications for an emergency cholecystectomy include emphysematous cholecystitis, gallbladder necrosis, and perforation[23].

Acute abdomen poses a diagnostic challenge, especially in the setting of lupus. Though rare clinicians should always have a high index of suspicion of lupus associated ACC due to its high mortality rates, one should suspect it if a lupus patient presents with fever, abdominal pain, leukocytosis, and elevated liver tests. Lupus activity tests such as anti-double stranded DNA and complement levels can help augment the diagnosis. Imaging should be interpreted in the context of the clinical presentation of the patient. There is evidence from literature that a majority of the gall bladder abnormalities have low sensitivity rates.

Conclusions

This case demonstrates there may be a role of corticosteroid therapy for lupus associated ACC. There is limited research on the comparison of the effectiveness of corticosteroid treatment with surgery due to low numbers of lupus associated ACC cases. The decision to treat either conservative or surgery should be tailor-made to each patient. There is evidence that supports patients in good general condition, having no severe complications (such as emphysematous cholecystitis, gallbladder necrosis, and perforation), has no other risk factors for ACC and no evidence of infection can benefit from high dose corticosteroids (0.5–1.5mg per kilogram of body weight per day for 3-5 days) as first-line treatment. More research still needs to be done on this rare manifestation of lupus. The need for the surgical and rheumatology teams to work together is paramount to improve outcomes of patients with lupus associated ACC.

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Lupus myocarditis, a reversible cause of heart failure in sub-Saharan Africa: a case report

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Abstract

Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disease with multisystemic involvement and varied clinical courses. It has a predilection for women in their reproductive ages. It is more common in sub-Saharan Africa than was previously reported. While pericarditis is a relatively common cardiac manifestation of lupus, myocarditis is a rare but potentially life-threatening manifestation. Myocarditis may present as heart failure amid other multisystemic manifestations. Therefore, a high index of suspicion is required for early diagnosis and prompt management to prevent fatal complications. We hereby present a 24 year old female who presented at our rheumatology clinic with generalized lymphadenopathy and inflammatory polyarthritis. She subsequently defaulted clinic follow-up until she presented five months later at the emergency department with sepsis, serositis, lupus myocarditis, and acute heart failure with reduced left ventricular ejection fraction. She was commenced on intravenous antibiotics and within days of methylprednisolone therapy, she experienced a dramatic improvement in her cardiac symptoms.

Key words: Systemic lupus erythematosus, Myocarditis, Heart failure, Sub-Saharan Africa

Introduction

Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disease that is characterized by inflammation of multiple organ systems with a myriad of clinical manifestations. Cardiac involvement is found in about 50% of patients with lupus, affecting the heart components[1,2]. However, myocardial involvement is relatively rare and may present as heart failure with associated extracardiac manifestations[1,2]. The frequency of myocarditis presenting as acute heart failure is rarely reported in sub-Saharan African studies on heart failure probably because these studies focused only on chronic heart failure. The important causes of heart failure in those studies include hypertension, cardiomyopathies, rheumatic heart disease, endomyocardial fibrosis, and HIV-induced cardiomyopathy[3,4]. The prevalence of SLE in sub-Saharan Africa according to a meta-analysis of recent studies shows that it is much higher than it was previously reported[5,6]. This is probably due to increasing diagnostic capacity, environmental factors (pollution, viruses, smoking, western lifestyle), and poverty[6]. In addition, SLE reported in sub-Saharan Africa also share some clinical and demographic characteristics with African descendants living outside Africa in terms of early age at diagnosis, female predominance, and protean manifestations including myocarditis[6,7]. Therefore, the purpose of this case report is to raise awareness of lupus myocarditis as an important reversible cause of acute heart failure in sub-Saharan Africa.

Case report

The index case is a 24 year old woman who presented in March, 2019 at the Rheumatology Clinic of the Department of Medicine, Obafemi Awolowo University Teaching Hospitals Complex (OAUTHC), Ile-Ife on account of progressive and painless right post-auricular swelling and multiple inflammatory joint pains involving her toes, ankles, feet, knees, wrists, elbows, shoulders, metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints with associated swelling in the affected hand joints, ankles, and wrists. She also had low-grade fever, but no fatigue or weight loss. Other systemic history was insignificant. She was not a known hypertensive or diabetic. There was no family history of autoimmune disease.

General physical examination showed non-tender, mobile, and rubbery axillary and inguinal lymphadenopathy. There was also a mass on the right side of her neck, in the post-auricular area, measuring 4cm by 4cm, non-tender, mobile, and rubbery, perceived to be

an enlarged lymph node. Musculoskeletal examination findings were in keeping with inflammatory polyarthritis of the affected joints. Examination of other systems was essentially normal. An assessment of SLE was made to rule out lymphoma, rheumatoid arthritis, and viral polyarthritis.

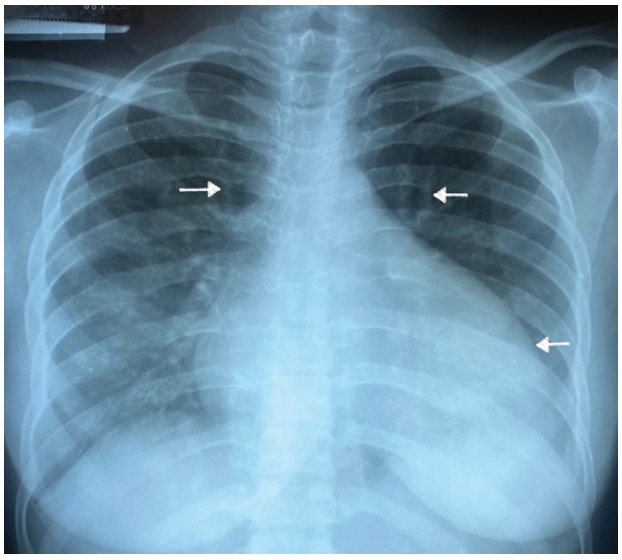
Complete blood count showed Packed Cell Volume (PCV) of 30% and the Erythrocyte Sedimentation Rate (ESR) was 132mm/hr. C-Reactive Protein (CRP) was also raised, 45.3-g/L (0 -10-g/L). Plain hand radiograph, viral screening, serum electrolytes, urea, and creatinine; urinalysis, and urine microscopy were all normal. Antinuclear Antibody (ANA), Anti-double stranded Deoxyribonucleic Acid (Anti-dsDNA), Rheumatoid Factor (RF), anti-Cyclic Citrullinated Peptide (Anti-CCP), and biopsy of the neck mass were ordered but the patient declined.

The patient was lost to follow-up until she presented five months later with high-grade fever, watery diarrhoea, nocturnal cough productive of whitish sputum, exertional dyspnoea, orthopnoea, and paroxysmal nocturnal dyspnoea. There was no associated abdominal or leg swelling, no history of exercise intolerance or post-exertion squatting in childhood.

Respiratory examination revealed tachypnoea, and coarse crepitation in the middle and lower lung zones bilaterally. Cardiovascular examination revealed tachycardia, displaced apex beat in the left 6th intercostal space, anterior axillary line, diffuse, with S1, S2, and S3 gallop rhythm.

Repeat full blood count showed PCV of 20.6%, leucopenia (3700/μL), and lymphopenia (700/μL). Sputum, blood, urine, and stool culture yielded no growth. Serum procalcitonin was highly elevated. Chest radiograph showed cardiomegaly with upper lobe diversion of vascular markings and non-homogeneous opacities in the right middle and lower lung zones, and mild left-sided pleural effusion (Figure 1).

Figure 1: Chest plain radiograph on admission showing cardiomegaly and upper lobe diversion of vascular markings



Electrocardiogram (ECG) showed sinus tachycardia, left atrial enlargement, left ventricular hypertrophy, and widespread T-wave inversion in anterolateral leads (Figure 2). Echocardiography revealed mild pericardial effusion, dilated left ventricle with hypertrophied interventricular septum and the left ventricular posterior wall, reduced Left Ventricular Ejection Fraction (LVEF) of 30%, and left ventricular diastolic dysfunction. The heart valves were normal. Antinuclear antibody titre was 1:5120, Anti-ds-DNA was> 200 (0 – 25U/ml). Rheumatoid factor and anti-CCP were negative. A lymph node biopsy showed no evidence of lymphoma. Fasting lipid profile, fasting blood glucose and two-hour postprandial glucose were also normal.

Figure 2: ECG on admission showing left ventricular hypertrophy, left atrial enlargement, and T-wave inversion of the anterolateral leads

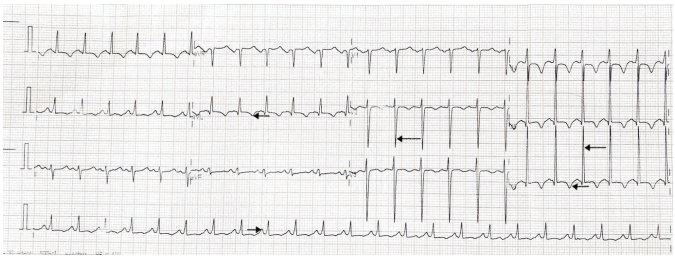
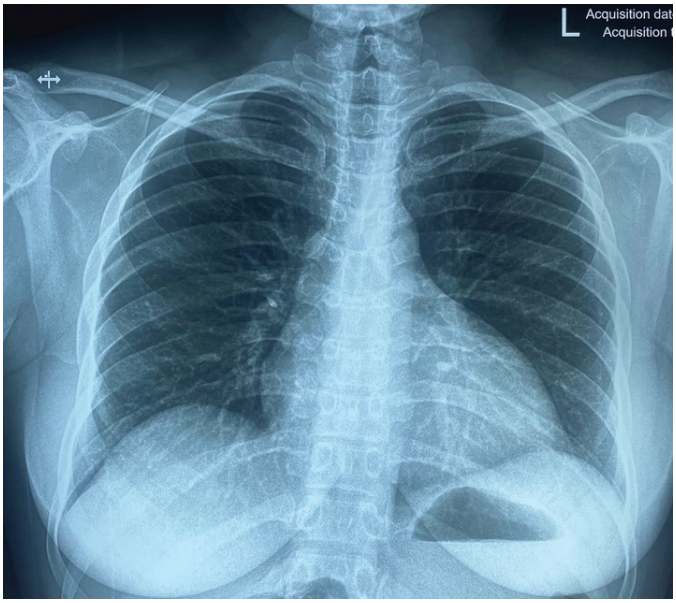


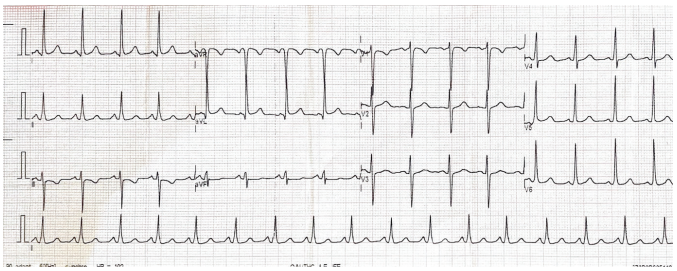
Figure 3: Repeat chest plain radiograph at 3 year follow-up showing dramatic structural reversal of the earlier changes



Using the 2012 Systemic Lupus Erythematosus International Collaborating Clinics Criteria (SLICC), a diagnosis of SLE complicated by heart failure with reduced ejection fraction(New York Heart Association class IV) and sepsis from chest focus was made. She was treated with intravenous antibiotics for sepsis with serial serum procalcitonin monitoring while anti-failure regimen with oral spironolactone, telmisartan, frusemide, and bisoprolol was commenced. The patient had two pints of blood transfused and was pulsed with methylprednisolone

500mg daily for three days followed by oral prednisolone, intravenous cyclophosphamide regimen for induction therapy, and then oral mycophenolate mofetil for maintenance therapy. Within a week after completing pulse steroid therapy, there was a dramatic improvement in her cardiac symptoms and she was subsequently discharged for follow-up. Echocardiography was repeated 6 months later and was completely normal with LVEF of 58%. Anti-failure regimen was then discontinued and serum anti-dsDNA was serially monitored until it was normal. She is presently on low-dose prednisolone, hydroxychloroquine, azathioprine, and calcium/vitamin D supplement. The generalized lymphadenopathy has also completely resolved. Repeat chest radiograph and ECG that were done on follow-up showed signs of significant improvement (Figures 3 and 4).

Figure 4: Repeat ECG, done at 3 year follow-up showing complete normalization of the earlier changes



Discussion

Systemic Lupus Erythematosus (SLE) is a chronic autoimmune, multisystemic connective tissue disease characterized by the elaboration of auto-antibodies targeting nuclear antigens, highly variable clinical presentations, disease course, and prognosis[8]. The global prevalence of SLE ranges from 20 – 70 per 100,000 with a higher prevalence in African Americans and a female-to-male ratio of 7-15:1[8,9]. Cardiac manifestations in SLE can involve the pericardium, myocardium, endocardium or valves, coronary arteries, and the conducting system[2]. While pericarditis is the commonest cardiac manifestation of lupus, myocarditis is a rare, life-threatening condition, presenting as acute heart failure and it usually occurs as part of generalized lupus activity[2,10]. Clinical lupus myocarditis usually presents with fever, dyspnoea, tachycardia, and congestive heart failure. The most common features include left ventricular dysfunction, non-specific ST/T-wave changes, segmental wall motion abnormalities, and decreased ejection fraction found in >80% of patients with myocarditis[11]. Other features include cardiomegaly, diastolic dysfunction, arrhythmias, and conduction defects[12,13]. In addition, left ventricular hypertrophy with/without atrial hypertrophy or ectopic ventricular beat could be an important feature of lupus myocarditis among black Africans[14]. A study done in South Africa on lupus myocarditis suggested that absolute lymphopenia and reduced LVEF at presentation were predictors of mortality[7]. Anti-Ro (SSA) and anti-RNP have been associated with lupus myocarditis[12,15]. Furthermore, markers of myocardial injury such as troponin I and creatine kinase may be raised in lupus myocarditis with the former being more sensitive[16]. Coronary artery disease in this patient is unlikely considering the age and absence of the traditional risk factors and classical features. Patients usually respond dramatically well to pulse steroid and strong immuno suppressives such as cyclophosphamide, mycophenolate mofetil, and rituximab with favourable outcome as it was with this case[10,12].

Anaemia of chronic disease, increased ESR, serositis, inflammatory arthritis, and lymphadenopathy are common manifestations of SLE and usually indicate an active disease[11]. Studies in Africa show that while polyarthritis, serositis, and alopecia are common presentations in lupus patients, skin manifestations are not as common as was reported in the literature[5,17]. SLE is an immunosuppressive disease; therefore, patients with active disease are predisposed to infection with both typical and atypical pathogens. Causes of immunosuppression in lupus include CD4 lymphopenia and immunosuppressive drugs. Infection is a major cause of mortality in SLE and therefore, it should be aggressively managed[6,11]. Although there are conflicting reports about the correlation between CRP and lupus activity, CRP is elevated in arthritis, serositis, lupus nephritis, and myocarditis.

Antinuclear antibody is a useful screening test for connective tissue disease because of its high sensitivity (>90%). However, it has a low positive predictive value for SLE because of its lower specificity. However, anti-dsDNA is highly specific (>95%) for lupus[11].

Lupus myocarditis is associated with high mortality. The newer and highly sensitive non-invasive imaging modalities such as cardiac magnetic resonance imaging, speckle tracking echocardiography, and 18F-fluorode oxyglucose positron emission tomography are emerging in the diagnostic evaluation of both clinical and subclinical forms of lupus myocarditis. It remains to be seen whether subclinical myocarditis is a predictor of fulminant myocardial disease or if early therapeutic intervention can modify the disease course and prevent the evolution of a clinical disease[7,18].

Limitations of this study include the inability to obtain echocardiographic images for this case report due to the limited memory of the echocardiographic machines. Furthermore, other important diagnostic investigations such as cardiac enzymes and connective tissue disease screening panel could not be done due to financial constraints and poor insurance coverage in a poor resource setting.

Conclusions

Systemic lupus erythematosus is the commonest connective tissue disease in black Africans and emerging studies in sub-Saharan Africa suggest that its prevalence may be similar to that reported among African-Americans. Furthermore, lupus runs a more aggressive course among

black Africans which correlates with the finding that the African-American race is an independent risk factor for lupus myocarditis. Therefore, lupus myocarditis should be considered especially in a young black woman who presents with florid symptoms of acute heart failure with extra cardiac manifestations in the absence of traditional risk factors for heart failure. SLE is a multisystemic disease that requires a multi-disciplinary approach to management to optimize outcome. Lupus myocarditis is a reversible cause of heart failure among black Africans if diagnosed early and prompt therapeutic intervention is instituted. The outcome of treatment is generally favourable and life-saving.

Disclosure: The authors hereby disclose no conflict of interest in writing this case report.

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CONTENT

Disease activity and adherence to disease modifying anti-rheumatic drugs among rheumatoid arthritis patients attending the Kenyatta National Hospital rheumatology clinic

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Abstract

Background: Disease activity among Rheumatoid Arthritis (RA) patients in Kenya has been found to be high in spite of a majority of them being on Disease Modifying Anti-Rheumatic Drugs (DMARDs) treatment. Adherence to DMARDs can be challenging and multiple factors contribute to variable adherence to therapy leading to treatment goals not being met.

Objective: The aim of this study was to evaluate treatment adherence and clinical disease activity among rheumatoid arthritis patients attending the Kenyatta National Hospital rheumatology outpatient clinic.

Methodology: A descriptive, questionnaire based, cross-sectional study was carried out at the Kenyatta National Hospital (KNH) Rheumatology Outpatient Clinic (ROPC). The sample consisted of patients over the age of 18 years with a diagnosis of rheumatoid arthritis diagnosed according to the 2010 ACR criteria who had been on at least one DMARD for at least three months. A study proforma was used to collect patient information while the validated 5 item Compliance Questionnaire of Rheumatology (CQR-5) was administered to assess adherence. The Clinical Disease Activity Index (CDAI) was used to assess disease activity. Data was presented as measures of central tendency with means or medians with standard deviation for continuous data and as frequencies for categorical data. Bivariate analysis was carried out to detect predictors of adherence.

Results: Ninety seven patients were recruited, of whom 84.5% were female and the mean age was 53.9 years. The overall level of adherence was 49.5%. Low disease activity was found in 5 (5.2%) patients, while 85 (87.6%) patients and 7 (7.2%) patients had moderate and high disease activity, respectively. The only significant positive correlation with adherence was found to be an age of over 62 years (p=0.036).

Conclusion: Adherence to DMARD therapy and disease activity among RA patients attending the KNH ROPC were determined using simple and effective tools. The adherence level was lower than global averages and WHO recommendations while disease activity was high. A significant association was found between age greater than 62 years and adherence to DMARD therapy. Interventional studies are recommended to help identify suitable measures to combat non-adherence.

Key words: Rheumatoid Arthritis, Adherence, Disease Activity, Nairobi, CQR-5

Challenges in the diagnosis and management of systemic lupus erythematosus in Africa

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Abstract

Background: Disparities in the prevalence and outcomes of Systemic Lupus Erythematosus (SLE) among different ethnic groups are well described. Whilst SLE patients of African descent are thought to have more severe disease, little is known about resource availability to support care in Africa.

Methodology: Across sectional online questionnaire-based survey was conducted among specialists involved in SLE care, over a 3-month period, examining the resources available to manage SLE in each country.

Results: A total of 226 responses from 31 countries were received; 87 (38.5%) were dermatologists, 64 (28%) rheumatologists and 52 (23%) nephrologists. The majority of respondents were in university (56.2%) or state (24.8%) practice, caring for patients for a mean of 11.1, SD ± 8.9 years. Majority 144 (63.7%) of respondents saw between 1 to 9 patients in a month. Anti-nuclear antibody and extractable nuclear antigen tests were available to 79% and 75.7% of respondents respectively, while Antiphospholipid syndrome (APS) tests and complements levels to 67% and 61.9% of respondents. Urine microscopy and Urine Protein Creatinine Ratio (UPCR) were available to 82% respectively. Skin biopsy was accessible to 82.7%, renal biopsy to 76.5% and muscle biopsy to 51.3%. On average renal biopsy was available to 42% of respondents four weeks later and skin biopsy to 41% two weeks later. While corticosteroids and hydroxychloroquine were widely available, other immunosuppressants availability varied {methotrexate (93.8%), azathioprine (83%), mycophenolate mofetil (77%), intravenous cyclophosphamide (72.5%), calcineurin inhibitors (65%), rituximab (58.4%) and Benlysta (3.5%). Haemodialysis was available to (92%), and plasmapheresis to 55% of respondents. Less than 70% of participants had an ICU/high care facility and 56 % had renal transplant facilities

Conclusion: Diagnostic capabilities for SLE are limited across Africa and may lead to underestimation of prevalence. Management remains a challenge due to limited access to adequate therapeutic options and supportive care facilities.

Factors impacting the delivery of care for systemic lupus erythematosus patients in Africa

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Abstract

Background: Systemic Lupus Erythematosus (SLE) diagnosis and management are difficult, and little is known about the factors that influence care delivery and outcomes in SLE patients in Africa.

Methodology: Across sectional online questionnaire-based survey was conducted among specialists involved in SLE care, over a 3-month period to determine the factors that contribute to poor outcomes in SLE patients in Africa.

Results: A total of 226 responses from 31 countries were received; 87 (38.5%) were dermatologists, 64 (28%) rheumatologists, 52 (23%) nephrologists and the rest physicians and/or medical officers. Despite the majority of respondents being in university (56.2%) or state (24.8%) practice, patient care was largely funded privately (59%), with state and medical insurance contributing 19.4% and 11.5% respectively. While 40% of respondents indicated that patient support groups were available; 26.4% of respondents indicated they were unaware of the availability/ existence of such groups. The most commonly cited reasons for late diagnosis were lack of awareness (92.4%) and lack of financial resources (80.1%), followed by a lack of access to care (61.9%), the use of traditional healers (55.3%), unavailability of diagnostic tests (51.7%), bewitchment (38.9%), and HIV co-infection (23.9%). Reasons cited for poor outcome were late presentation (95%), lack of resources (diagnostic tests and human) 91%, drug access (82.3%), lack of supportive service e.g. ICU (62%), infection (48%) and intrinsic aggressive disease in African patients (38%).Measures cited to improve care were: increased resources (91%), ongoing medical education (88.9%), specialist training (85.4%), patient education (84.5%) and undergraduate training (70.1%).

Conclusion: SLE diagnosis and management in Africa are hampered by a lack of awareness and resources. To improve the outcomes of this potentially fatal disease in Africa, concerted efforts must be launched to address these issues.

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Impacts of disease activity on functional disability in systemic lupus erythematosus patients

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Abstract

Background: Systemic Lupus Erythematosus (SLE) is a multi-systemic autoimmune disease characterised by flares and remissions. Flares due to multiple triggers often result in heightened disease activity, consequently affecting the patient's ability to carry out their activities of daily living.

Objective: To determine the impacts of disease activity on the functional disability of patients with SLE.

Setting: A hospital-based cross-sectional study of 55 patients satisfying the 2012 Systemic Lupus International Collaborating Clinics (SLICC) classification criteria for SLE recruited consecutively over nine months in the rheumatology clinic of Lagos State University Teaching Hospital, Nigeria.

Methods: The disease activity and functional disability were assessed using the Systemic Lupus Erythematosus Disease Activity Index-2000 (SLEDAI-2K) and the Health Assessment Questionnaire (HAQ) tools. Data were analysed using Statistical Package for Social Sciences (SPSS) version 25, and a p-value <0.05 was considered significant.

Results: The mean± SD age of all subjects was 34.3±10.3 years (range, 19-68 years). There were 51 (92.7%) females with a female-to-male ratio of 12.7:1. Skin manifestations (64.7%) and joint involvement (56.9%) were the most common clinical features seen. Hypertension was seen in 41.8%, while 38.2% had renal involvement. Forty-two (76.4%) had active disease, of which 14.5% had mild, 27.3% had moderate, 16.4% had high, and 18.2% had very high disease activity. Of 37 (67.3%) with activity limitations, mild, moderate, severe and very severe functional disabilities were seen in 29.1%, 25.1%, 10.9% and 1.8% of patients, respectively. Patients reported more activity limitations in the "walking" (49.1%) and "reach" (47.3) components of the HAQ tool. There was a strong positive correlation between disease activity and functional disability (r=0.84, p<0.001, coefficient of determination-70%).

Conclusion: The study showed that most SLE patients in the tertiary rheumatology clinic had active disease and functional disabilities. There is a positive correlation between disease activity and functional disability in these SLE patients.

Key words: Systemic Lupus Erythematosus, Disease activity, Functional disability

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Acne rosacea associated with Sjögren's syndrome: a case report

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Abstract

Background: Rosacea is a chronic relapsing dermatosis that affects millions of people throughout the world. The association between autoimmune disorder and rosacea has not been studied well including Sjögren's syndrome.

Case report: A 55-year-old housewife presented with itchy erythematous popular facial skin rash on her face and dry mouth, eyes, and skin for more than 2 years. She also complained from small joints of pain in both hands and feet. She was suffering from continuous fatigue. Other symptoms regarding musculoskeletal system were unremarkable. On examination she looked unwell, blood pressure was 110/70, pulse rate was 80, oxygen saturation was 98, and respiratory rate was 12. Her face showed a popular erythematous rash over malar area and nose and forehead.Investigation revealed high ESR, high C3, Anti-nuclear antibody titer of 1/160, and reactive Anti-SS-A/Ro -52. Skin biopsy confirmed the diagnosis of acne rosacea.

Discussion: Rosacea was once thought to be a skin-specific issue, but now there is growing evidence connecting it to systemic diseases. Recent research has indicated that rosacea sufferers have a higher risk of cardiovascular illness, allergies, mental issues, gastrointestinal difficulties, malignancies, and autoimmune conditions than do people without the condition.

Conclusion: This research highlights a rare association between acne rosacea and Sjögren's syndrome. Acne rosacea affecting the face can be mistaken for other autoimmune diseases and be differential to malar rash.

Key words: Acne Rosacea, Sjögren's syndrome, Case report

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Adult Onset Still's Disease with atypical cutaneous manifestation in a Nigerian female: case report

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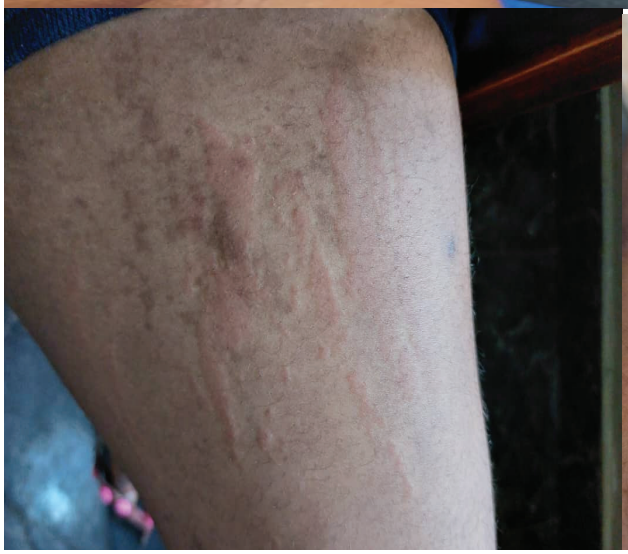
Abstract

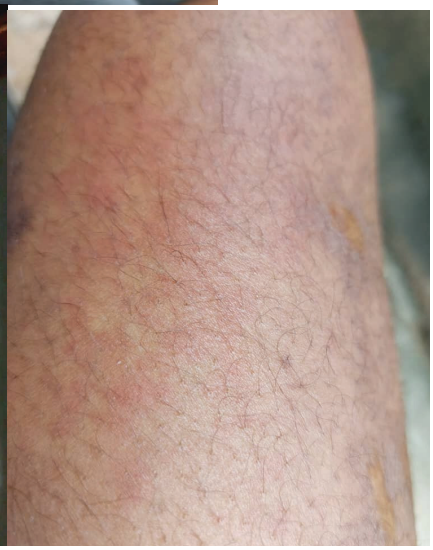
Background: Adult Onset Still's Disease (AOSD) is a rare systemic auto-inflammatory condition of unknown aetiology. It has bimodal age distribution and female preponderance. AOSD classically manifests as a triad of; daily high-rising fever often described as a quotidian or double quotidian fever, arthritis, and an evanescent salmon-pink maculopapular rash occurring mostly at the peak of fever. However, there are few reports of atypical persistent pruritic papules and urticarial in AOSD.

Objective: We report a case of AOSD with atypical cutaneous manifestation in a 26-year-old Nigerian female.

Case report: A 26-year-old female presented with two weeks history of high-grade fever, arthritis of the knees, and widespread persistent erythematous maculopapular and urticarial rashes over her thighs, arms, and forearms. She was initially diagnosed with septic arthritis for which she had an IV meropenem administration. Her laboratory tests showed a packed cell volume of 38%, white cell count of 15600 with predominant neutrophil (85%), platelet count of 486000, erythrocyte sedimentation rate of 145mm/hour, C-reactive protein 235mg/L, and serum ferritin of 13300ng/L. Other tests to exclude infections, malignancies and other rheumatic autoimmune conditions were negative.She was initially treated with IV pulse methylprednisolone 500mg daily for three days thereafter, oral prednisolone 30mg daily, sub-cutaneous methotrexate 15mg weekly then later oral methotrexate at 17.5mg weekly, and folic acid 10mg weekly. She made remarkable improvements with a resolution of her clinical symptoms and inflammatory markers but has the persistence of the urticarial rashes.

Conclusion: AOSD may present with atypical cutaneous manifestations. Therefore, a high index of suspicion is required to identify such variants.





Rheumatoid arthritis with coexisting thyrotoxicosis: a case report

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Abstract

Background: There are few reports in literature of the coexistence of rheumatoid arthritis and thyrotoxicosis.
Objective: We present a case of rheumatoid arthritis and degenerating multi nodular goitre presenting concurrently and acutely with constellation of symptoms and signs that initially made management challenging.
Case report: A 40 year old Nigerian lady presenting simultaneously with poly symmetrical inflammatory arthritis with decreased range of movement in both knee, significant fatigue, fever, weight loss, palpitation and excessive sweatiness. Examination was significant for anaemia, pyrexia, positive squeeze test and rheumatoid nodule with a Clinical Disease Activity Index (CDAI) of 24. Her laboratory tests results were as follows: Erythrocyte Sedimentation Rate (ESR) 102 mm/hr, C-reactive protein was 94mg/L, Hb, 7.5g/dl fasting blood sugar 5.2 mg/dl, rheumatoid factor 85.6 IU/ml, Anti CCP 88.7 U/ml TSH <0.1 T3 6.1 ng/ml T4 23.3µg/ml ECG sinus tachycardia with heart rate of 108 bpm. Her neck ultrasound scan revealed degenerating multi nodular goitre and plain hand X-ray showed erosive arthritis. She was commenced on steroids, naproxen, methotrexate, hydroxychloroquine, carbimazole and propanolol, Due to significant knee inflammatory arthritis she had arthrocentesis with intra articular steroids in both knees. Patient improved with CDAI score of 10, ESR of 40 and was subsequently discharge for follow up clinic visits.
Conclusion: It is worthwhile to screen rheumatoid arthritis patients presenting with numerous extra articular and constitutional symptoms, for autoimmune clusters especially thyroid to mitigate worse outcomes and missed diagnosis.

Real world trends for clinical remission and the characteristics of difficult to treat patients with rheumatoid arthritis in the academic center in Tokyo

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Abstract

Background: Primary target of Rheumatoid Arthritis (RA) treatment as clinical remission in Treat-to-Target was globally well recognized since 2010. However, the data from real world were still limited.

Methods: In order to investigate the trend in the rate of clinical remission in RA patients in one of the centers of excellence in APLAR, we retrospectively surveyed the charts at year 2011 (n=1408), 2014 (n=1498), and 2018 (n=1693). Clinical characteristics of difficult-to-treat RA (D2T-RA) in most recent survey for RA (n=1709) was analyzed in detail.

Results: Clinical remission was 46, 41, and 31, respectively (DAS28-ESR, CDAI, and Boolean), in 2011, 61, 53, 40, respectively, in 2014, and 65, 64, and 48, respectively in 2018. The remission rate was increased, irrespective of remission criteria used. In 2018 cohort, DAS28-ESR remission was 63.9%, 71.0%, and 67.8% in csDMARDs, first b/tsDMARDs, and second b/tsDMARDs treatment of RA, showing comparable remission rate among different treatment timings. However, remission rate was apparently reduced from third or more b/tsDMARDs, consistent with the sequencing in current recommendations/ guidelines proposed by regional and national society. About 10% of RA patients fulfilled criteria of D2T-RA by EULAR, with longer duration of disease and time to start first b/tsDMARDs, seropositivity, admission history due to infection, lung co-morbidity. In addition, 5% of patients had moderate/high disease activity even without fulfillment of D2T-RA. These patients were older, contra-indications for MTX, co-morbidities, and having infection, with only 0.6 of the average number of b/tsDMARDs used.

Conclusion: By implementation of Treat-to-Target in real world, remission was apparently increased during the past 10 years. Still, at least about 15% did not achieve treatment target. By looking at the remission rate among APLAR countries (Sun X, *et al. Lancet Regional Health* 2021), we should understand background and unmet-needs, and improve treatment strategy further in RA.

Identification of novel autoantibody biomarkers in systemic lupus erythematosus using microarray immunoproteomics

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Abstract

Background: Systemic Lupus Erythematosus (SLE) is a multisystem autoimmune disease with diverse manifestations. Increased autoantibody concentrations is the hallmark of SLE pathogenesis, and are typically present years prior to diagnosis. Protein microarrays are capable of simultaneously characterising the biomolecular interactions of thousands of proteins, thus making them ideal tools for autoantibody profiling in SLE clinical phenotypes.
Objective: To identify novel autoantibody proteomic signatures in SLE patients plasma using protein microarrays, with potential to improve diagnostics and patients stratification.
Methods: SLE patients were recruited from rheumatology clinics at an academic hospital in Cape Town. We investigated IgG and IgA autoantibody responses: first, in pooled plasma from 18 SLE patients and matched controls against 1600+ proteins on the Sengenicsi-Ome protein microarray, and second, in individual participant plasma against 50 antigens on an autoimmune disease-focused microarray. Raw data were imported and analysed using R (Version 4.0). Analyses identified autoantibody signals 2-SD above the average signal from controls, followed by Student's t-test and clustering analyses.
Results: SLE patients were aged 34±9 years, 89% were women, racial distribution was either mixed (67%) or black African (33%) ancestry. Median disease duration was 5(IQR:3-8) years and patients had moderate disease activity (median SLEDAI-2K score=7, [IQR:4-12]); and low damage scores (median SLICC-DI=1, [IQR:0-1]). Pooled plasma from SLE patients on the i-Omemicroarray showed significantly increased IgG and IgA responses relative to controls against 20 and 157 proteins, respectively. On the autoimmune microarray, 16 proteins showed significant IgA responses (Table 1), and these candidate biomarkers demonstrated clear separation between SLE patients and controls on both hierarchical clustering (Figure 1) and principle component analyses (Figure 2).
Conclusions: We demonstrate differential autoantibody expression in SLE patients compared to controls. A larger number of proteins elicited IgA responses compared to Ig Gin SLE plasma on both microarrays. Autoantibody signatures may serve as future diagnostic, therapeutic and prognostic biomarkers in patients with SLE.

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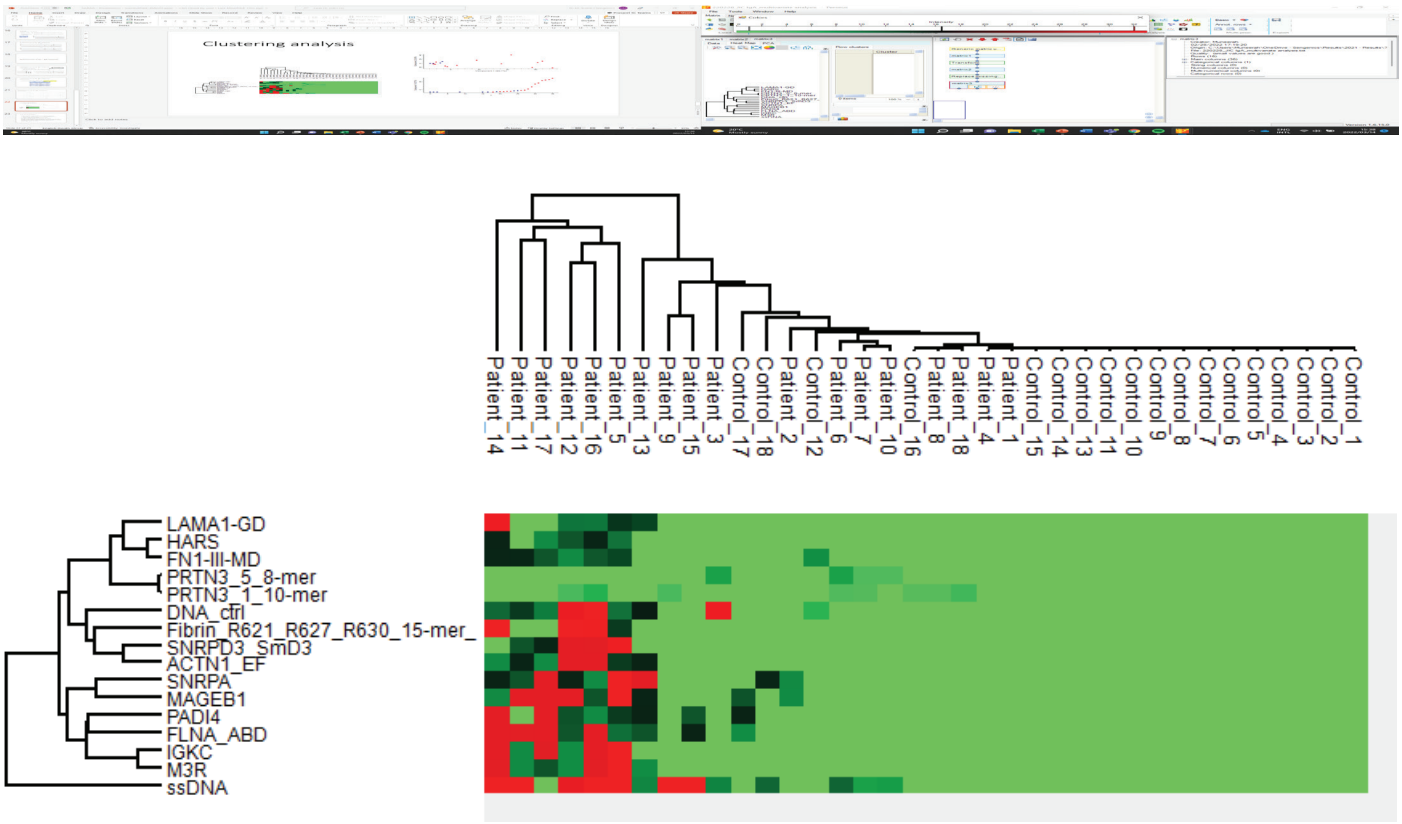
Table 1: Proteins that showed significant IgA autoantibody responses on the autoimmune microarray

Protein	P-value
ssDNA	0,008
M3R	0,016
ACTN1_EF	0,017
FLNA_ABD	0,017
PRTN3_1_10-mer	0,023
MAGEB1	0,025
IGKC	0,025
PADI4	0,027
FN1-III-MD	0,027
LAMA1-GD	0,027
DNA_ctrl	0,028
SNRPA	0,029

Protein	P-value
SNRPD3_SmD3	0,036
PRTN3_5_8-mer	0,042
Fibrin_R621_R627_R630_15-mer_	0,043
HARS	0,046

Figure 1: Hierarchical clustering analysis of 16 proteins with significant IgA responses on the autoimmune microarray



Characterising the phenotype of subclinical cardiovascular disease in systemic lupus erythematosus using multiparametric cardiovascular magnetic resonance imaging

Bana TM[1,2], Samuels P[3], Jermy S[3], Kraus S[1], Ntusi NAB[1,2,3]

Abstract

Background: Cardiovascular disease (CVD) is a leading cause of morbidity and mortality in Systemic Lupus Erythematosus (SLE) but data from Africa are lacking.

Objective: We conducted a cross-sectional study to characterise subclinical cardiovascular (CV) involvement in SLE using Cardiovascular Magnetic Resonance (CMR).

Methods: Forty nine SLE patients without known CVD, recruited from rheumatology clinics in Cape Town,were compared to 24 matched controls. All participants underwent multiparametric CMR at 3 Tesla, including cine, T2-weighted, Late Gadolinium Enhancement (LGE), native and postcontrast T1 mapping, ECV quantification and strain imaging. Clinical and demographic data were recorded. Groups were compared using Fisher's exact and Student's t-test and regression analysis explored relationships between variables.

Results: SLE patients were aged 35±9 years, 90% were women and majority were of mixed (69%) or black African (27%) ancestry. Median disease duration was 5(IQR:3-8) years. SLE patients had moderate disease activity (median SLEDAI-2K score=7, [IQR:4-11]) and low damage scores (median SLICC-DI=1,[IQR:0-1]). Hypertension, smoking, and dyslipidaemia were present in 29%, 23% and 8%, respectively. Forty eight percent were on corticosteroid treatment, 43% were on methotrexate. Forty two (86%) SLE patients had evidence of subclinical CVD on CMR with myocardial involvement being the predominant manifestation seen in 38(78%) and pericardial effusions in 13(27%) patients. Mean LVEF was 57±7%, however, 21(43%) SLE patients had evidence of mild systolic dysfunction (LVEF:47-56%). SLE patients had significantly increased native myocardial T1 and ECV fraction values (Figure 1) indicative of myocardial fibrosis. Focal fibrosis detected by LGE was present in 37(79%,n=47) SLE patients. Myocardial strain was significantly impaired in SLE patients (peak longitudinal strain in SLE -15.4 vs. -17.4 in controls; p<0.001; Table 1) and correlated with decreasing LVEF and increasing native T1 and ECV values.

Conclusions: We demonstrate high prevalence of subclinical CV involvement in young ethnically diverse SLE patients in South Africa, with moderate SLE disease activity. Myocardial involvement was frequently observed in SLE compared to controls, including significant differences in structural and functional parameters, tissue characteristics, and myocardial strain.

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Figure 1: Native T1 and ECV fraction in SLE patients and controls

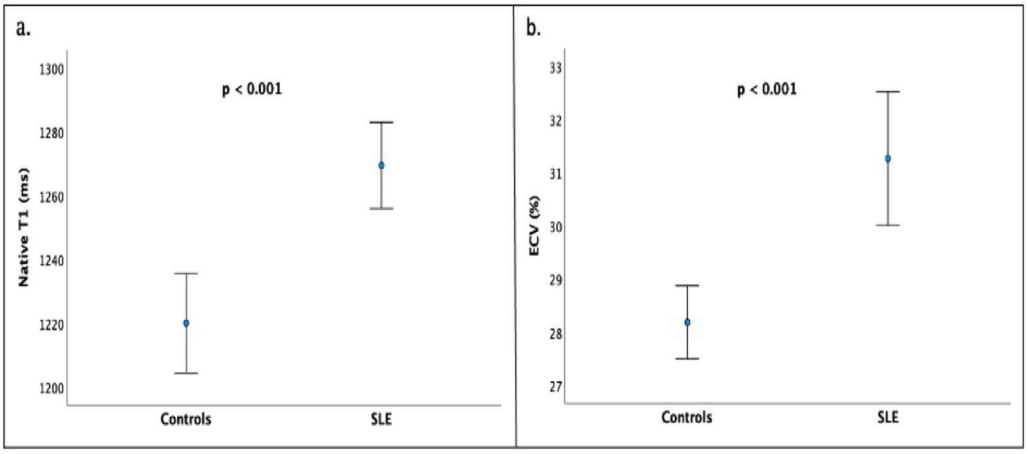

Table 1: Comparison of CMR parameters in SLE patients and controls

	SLE patients (n = 49)	Controls (n = 24)	P- value
Age, years	35 ± 9	37 ± 10	0.369
Female sex, n (%)	44 (90)	22 (92)	0.799
LVEDV indexed to BSA, ml/m^2	80 ± 18	71 ± 7	0.002
LVESV indexed to BSA, ml/m^2	35 ± 14	28 ± 5	0.002
LVEF, %	57 ± 7	60 ± 5	0.066
LV mass indexed to BSA, g/m^2	51 ± 9	45 ± 6	0.002
Peak longitudinal strain	-15.4 ± 2.3	-17.4 ± 1.9	< 0.001
Peak diastolic radial strain rate (s-1)	-2.0 ± 0.8	-2.3 ± 0.5	0.05
Peak diastolic longitudinal strain rate (s-1)	0.9 ± 0.2	1.1 ± 0.3	0.02
Global myocardial T2 SI ratio	1.5 ± 0.3	1.6 ± 0.2	0.67
Native myocardial T1, ms	1269 ± 47	1220 ± 37	< 0.001
ECV (%)	31 ± 4.3	28 ± 1.6	< 0.001
Presence of LGE, n (%) (n= 47 SLE, n= 23 controls)	37 (79)	10 (43)	0.003
LGE %	31 ± 7	23 ± 6	< 0.001

Continuous data are mean ± SD unless otherwise indicated. BSA, body surface area; ECV, extracellular volume; LGE, late gadolinium enhancement; LV, left ventricle/ventricular; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; SLE, systemic lupus erythematosus.

Sjögren's syndrome in a Sudanese patient with vascular Ehlers-Danlos syndrome: a case report

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Abstract

Background: This case presents a rare association between Sjögren's syndrome and vascular type Ehlers-Danlos syndrome. Some evidence exists for increased incidence of autoimmune disorders, such as rheumatoid arthritis, systemic lupus erythematosus and Sjögren's syndrome in Ehlers-Danlos syndrome.

Case report: A thirty two year-old Sudanese female resident in Ireland presented to our facility complaining of photosensitive skin rash on the cheeks and nasal bridge, easy bruising and bluish discoloration of the fingers when exposed to cold and stress since childhood. She often bruised easily even with minor trauma and her wound were slow to heal, with no history of bleeding from any site. She had infrequent attacks of arthritis affecting the small joint of the hands and sometimes shoulders and hips, with mild restriction of movement. She also had proximal muscle weakness in both upper and lower limbs. In addition, she observed that her joints are hypermobile and her skin is hyperplastic. This patient had a history of recurrent sternoclavicular joint dislocations with Brighton score of 6 and family history of same condition. She had a history of recurrent oral ulcers, genital ulcers, and one attack of blurring of visions and eye redness resolved by eye drops after which she was diagnosed with Bahcet disease. She was known to be allergic to ciprofloxacin and currently she is on mycophenolatemofetil 500mg twice per day, bosentan 62.5mg once per day, pentoxyphyline 400mg twice per day. Investigations revealed slightly raised C4 level and positive anti-CCP antibodies and anti-SS-B antibodies.

Conclusion: We present a rare case of Sjogren's syndrome in patient with Ehlers-Danlos Syndrome. This coexistence was not well studied in the literature.

Key words: Sjögren's syndrome, Ehlers-Danlos syndrome, Case report

Prevalence and impact of fibromyalgia in patients with systemic lupus erythematosus

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Abstract

Background: Fibromyalgia is an increasingly recognized medical disorder characterized by chronic widespread musculoskeletal pain, fatigue, and poor sleep. The association of fibromyalgia and lupus has been studied widely and it is conceivable that they may influence each other. The aetiology of both the disease is unknown and the overlapping symptoms of lupus and fibromyalgia can lead to misinterpretation of lupus activity and risk of overtreatment. No studies of this association have been held in the black African population, bearing in mind the nature of the influence of chronic disorders on quality of life and disease activity. Understanding the nature of this association in our population may contribute to this discussion.

Objectives: To determine the prevalence and impact of fibromyalgia in patients with Systemic Lupus Erythematosus (SLE) attending the rheumatology clinic at the Kenyatta National Hospital (KNH).

Methods: This was a cross-sectional descriptive study of SLE patients in Kenyatta National Hospital, rheumatology clinic. SLE patients with musculoskeletal pain were screened for fibromyalgia using the revised 2010 ACR criteria, those who fulfilled the criteria were diagnosed with fibromyalgia and subsequently given FIQR questionnaire to assess the severity of their symptoms. The disease activity was assessed using SLEDAI-2K. A self-administered SF-36 questionnaire was used to evaluate the quality of life. Categorical data of the study population were summarized into proportions and continuous variables were summarized into means, medians, and SD. The prevalence of fibromyalgia is presented as a percentage. The severity of fibromyalgia was presented as a proportion in each class (mild, moderate, and severe). The QoL score was calculated and presented as proportions for good and poor. Disease activity was scored and categorized into mild, moderate, and severe diseases, and then presented in percentages. A p-value of ≤ 0.05 was considered significant.

Results: The study group comprised of 60 patients, all female with a mean age of 34 years. The prevalence of fibromyalgia among SLE patients was 65% (n= 39). All domains of HRQoL were impaired. The mean score of the 8 domains were; Physical function 30.6±19.2, physical health 3.2±8.5, emotional problems 15.4±36.6, fatigue 32.1±12.5, social function 39.5±16.3, emotional well-being 39.4±18.0, pain 39.7±12.7 and general health 30.6±19.2. The median SLEDAI score was 7.0 (IQR 4.0-10.0), with half of the patients having moderate–severe disease activity (51.3%). Patients with fibromyalgia were more likely to be on steroids than non-fibromyalgia (p-value< 0.05). Other factors like marital status, nature of employment, and age were not found to be statistically significant.

Conclusion: Fibromyalgia is prevalent in SLE patients presenting with chronic pain, in their middle age. The majority of the patients have moderate disease activity. The presence of fibromyalgia adversely impacts the quality of life of patients with lupus.

Impact of living with lupus as perceived by patients and their self-management strategies

Omondi EA, Caress A[2], Cooke H[3], McHugh G[4]

Abstract

Background: Lupus is a chronic, autonomic, multisystem disease that predominantly affect women of child bearing age. Lupus is believed to have both physical and psychological impact on affected individuals. However, there is paucity of data on the impact of living with lupus and the self-management strategies employed by patients in Kenya.
Objective: To explore how living with lupus has affected the patients' lives and identify their self-management strategies.
Design: A generic qualitative approach with principles of constructivist grounded theory.
Setting: Two rheumatology clinics in Nairobi, one private and one public health facility.
Methods: Participants were identified using purposive and theoretical sampling techniques. Face to face interviews were conducted to obtain data. Interviews were transcribed verbatim and analysed inductively using the constant comparative method.
Results: The study revealed a key category of "A shadow of myself" and three sub-categories of loss of self, biographical disruption and biographical reconstruction. The findings revealed that the illness disrupted individuals' lives in various ways. However, they attempted to reconstruct their disruptions with variable success.
Conclusion: The study revealed that living with lupus was disruptive to individuals who previously had orderly lives and the need to support them, for meaningful life reconstruction.

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Investigating disease activity changes in Ghanaian autoimmune rheumatic conditions receiving Covid-19 vaccine

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Abstract

Background: Vaccines are crucial component of the global efforts to control the spread of Covid-19. Very little is known about the Covid-19 vaccine responses in patients living with autoimmune rheumatic conditions in Africa.
Setting: This was a hospital-based study
Methods: We conducted a prospective cohort study among Systemic Lupus Erythematosus (SLE) and Rheumatoid arthritis (RA) patients at the Korle Bu Teaching Hospital over one year period, recruited via their regular face-face clinic visits. Vaccines administered were Astra Zeneca and Pfizer with each participant receiving two doses per protocol. The SLE Disease Activity Index (SLEDAI Hybrid) and Disease Activity Score DAS 28 scores were used to measure disease activity.
Results: Thirty-eight patients were recruited, 21 (55.3%) had SLE and 17(44.7%) had RA. Majority (89.5%) were females. Average age was 37.4 years. At baseline, 52.4%, 28.6% and 19% of SLE patients had mild to moderate, severe and zero activity respectively, whereas 70.6%, 17.6% and 11.8% of RA patients had low to moderate, high and remission levels respectively. Severe flare increased by 4.8%, 9.5%, 20%, 9.5% at 3 weeks, 6 weeks, 3 months and 6 months respectively for SLE patients, and so is zero activity by 4.8%, 14.3%, 4.8% and 9.6% respectively, however both levels decreased by 7.5% and 3.2% respectively at 12 months. For RA patients, high disease decreased by 11.7% at 3 weeks, 5.8% at 6 weeks, 11.3% at 3 months and then to 0% at 6 and 12 months. However, remission levels increased by 17.6%, 11.7%, 13.2%, 13.2% and 7% at 3 weeks, 6 weeks, 3 months, 6 months and 12 months respectively.
Conclusion: There was steady increase of severe flare in SLE cases as well as zero activity level. Comparatively, high disease decreased steadily in RA patients and remission levels increased, showing that disease activity in RA patients improved after vaccination compared to SLE. Vaccine responses may vary by disease subtype and may influence disease outcome.

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Kenya registry of patients with rheumatic and musculoskeletal diseases with Covid-19 infections (KRMD-Covid registry)

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Abstract

Background: Patients with auto-immune diseases are hypothesized to have an increased risk for Covid-19 partly due to the immunosuppressive nature of the diseases and the medications used to control these conditions. We want to set out to understand the impact of Covid-19 on patients with rheumatic and musculoskeletal diseases

Objective: To document clinical characteristics and outcomes of rheumatic and musculoskeletal diseases patients with laboratory-confirmed Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) in Kenya

Methodology: The study included 55 patients with a confirmed PCR diagnosis of Covid-19 with rheumatic diseases between June 2021 and July 2022 at rheumatology clinics across Nairobi, Kenya. These had their data captured in a questionnaire and put up in registry. The data included socio-demographic, about their symptoms, Covid-19 testing, health care changes, and related experiences during the prior 2 weeks to diagnosis. Analysis compared responses by diagnosis, disease activity, and new onset of symptoms

Results: The population was female predominant (85.5%) with a mean age of 48.9 years and BMI of 26.11. Majority (83.6%) were on regular follow up at a rheumatology clinic. SLE was the most common diagnosis (32.7%), followed by RA (27.3%). Cough was the most common symptom (61.8%) followed by fever (52%), fatigue (43.6%) amongst others. Sixty one point eight percent were on DMARDs, 38.1% on steroids. There were two patients on biologics. The most common comorbids were hypertension (40%) and pulmonary disease (16.4%). Thirty percent were treated as inpatient with a mortality rate of 18.18%. The sample size was too small to draw any associations though there was a trend towards increased mortality amongst those with high disease activity.

Conclusion: Rheumatic patients with an increased risk for Covid-19 infection were female, high BMI and hypertensive. Mortality was high in this cohort especially amongst those with high disease activity.

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Metabolic syndrome in rheumatoid arthritis patients: prevalence and risk factors

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Abstract

Background: Rheumatoid Arthritis (RA) if untreated, has debilitating effects and is associated with increased risk of developing metabolic syndrome (Met-S). The prevalence of Met-S in people living with RA is, however, variably reported in different populations as is the frequency of the associated risk factors predisposing to the development of Met-S in RA. Nonetheless, hardly any local studies have been conducted to establish the burden of Met-S despite different socioeconomic and demographic factors that limit patients' access to quality healthcare.

Methods: A total of 127 patients with established RA were recruited and the following parameters measured/ calculated: sex, current age, age at diagnosis, level of education, medications, waist circumference, CRP/ ESR, BP, fasting lipid profile and blood sugar, HbA1C, disease duration, disease activity, ten-year risk for atherosclerotic cardiovascular disease, and presence of Met-S. Chi-square and Independent Student's t-test used were appropriately applied to determine differences between patients with Met-S and those without Met-S.

Results: The mean age, age at diagnosis and median duration of RA treatment was 51.48, 43.29 and 6.65 years respectively. Sixty five point four percent of patients had a waist circumference above the set cut off while 45.7% and 12.6% were overweight and obese respectively. Fifty three point five percent of the patients were hypertensive with 76.47% of these patients having uncontrolled BPs, 14.2% were diabetic while 29.9% had dyslipidaemia with 18.1% having elevated TG levels and 11.8% having low HDL levels. Of the RA patients, 55.12% of them had either moderate or high disease activity while 34.02% had a low 10-year CVD risk score with 52.58% had either intermediate or high risk scores. Twenty one point twenty six percent of the patients met the criteria for Met-S and were significantly older, had a later age of diagnosis and a longer duration of treatment ($p<0.001$). These patients had significantly greater SBP, WC, RBS, TC (all $p<0.001$), HbA1C ($p=0.012$), BMI ($p=0.002$), and TG ($p=0.003$).

Conclusions: Despite the local prevalence of Met-S being lower than the global average, the components of Met-S were however highly prevalent with sub-optimization of many of the modifiable risk factors predisposing the affected patients to a higher risk for CVD as reflected by the higher 10-year CVD scores in a majority of the patients. Greater emphasis during follow up should thus be accorded to RA patients in order to identify and adequately manage easily modifiable risk factors including obesity, HTN and dyslipidemia.

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Pain control and functional status in knee osteoarthritis

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Abstract

Background: Chronic pain in knee osteoarthritis influences the quality of life and functional status of these patients. Despite numerous treatment modalities, pain may be inadequately controlled and affect a patient's functional status. This may be more evident in our local setup as patients tend to present later in the disease. This study was designed to understand pain control in knee osteoarthritis.

Objective: To assess pain control and the level of function in patients with knee osteoarthritis at the orthopaedic and rheumatology clinics at the Kenyatta National Hospital.

Methods: A cross-sectional descriptive study that assessed patients above the age of 18 years with a diagnosis of knee osteoarthritis on follow-up who fit the inclusion criteria. The pain was assessed by the Brief Pain Inventory-Short Form (BPI-SF) and the functional status was assessed by the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). Any patient reporting a pain score >4 in question 5 of BPI-SF indicating moderate (4-7) or severe pain (>8) was classified as having inadequate pain control. Pain control was analyzed and presented as a proportion of patients achieving adequate pain control. Functional impairment was assessed using the WOMAC score (0-96). A higher score indicated poorer function. Pain severity was associated with functional status using the ANOVA test. The chi-squared test was used to associate patient-related factors with pain control. A 5% level of significance was used to interpret all the statistical tests (p-value less or equal to 0.05).

Results: A total of 270 patients were recruited into the study of whom 139 (51.5%) were females and 131 (48.5%) were males. The mean age of the study population was 55.1 years. The majority of the patients were overweight (n= 134, 49.6%) with a smaller number (n=27, 10%) being obese. The median duration of osteoarthritis diagnosis was 48 months. Bilateral knee osteoarthritis (n= 172, 63.7%) was more prevalent than unilateral disease (n= 98, 36.3%). Knee pain was inadequately controlled in 265(98.1%) participants with these patients scoring >4 (moderate to severe pain) in Question no 5 (pain on average) of the BPI-SF. The majority of participants (n=259, 95.9%) also had functional impairment/disability. Participants with inadequate pain control (moderate pain or higher) had a worse functional status p-0.026 (<0.05).Older patients had worse pain control p-0.029 (<0.05).

Conclusion: Pain control in knee osteoarthritis is mostly inadequate with most patients having a poor functional status. Inadequate pain control is associated with older age and a poorer functional status. This limits their daily activities and enjoyment of life.

Profile of spondyloarthropathy patients in Kano, Northwestern Nigeria

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Abstract

Background: Spondyloarthropathy (SpA) comprises a group of rheumatic conditions characterized by chronic inflammation especially of the spine and the entheses, with ankylosing spondylitis being the prototype of the group. Not much has been reported about spondyloarthropathy from the Northern part of Nigeria, particularly the Northwest which harbors about a quarter of Nigeria's population.

Objective: To report the profile of SpA patients seen in rheumatology clinics in Kano, Northwestern Nigeria.

Methodology: This was a hospital based retrospective study of all patients seen with a diagnosis of SpA over 12 years at rheumatology clinics of Aminu Kano Teaching Hospital (AKTH), National Orthopaedic Hospital Dala (NOHD) and Apex Consultants Hospital Ltd Kano. Data were extracted from the patient's case notes, and covers biodata, clinical data, laboratory data, as well as treatment offered to the patients.

Results: A total of 127 SpA patients were seen over the 12 year period. There were 81 cases of Ankylosing Spondylitis (AS), 21 were Juvenile AS, 11 were Reactive Arthritis (ReA), 2 were Psoriatic Arthritis (PsA), 4 were Inflammatory Bowel Disease (IBD) associated Arthropathy, with 8 cases of Undifferentiated SpA. Seventy-seven were males, and the overall average disease duration before diagnosis was 10.7 years. HLA-B27 was positive in 45% (32/70) of AS patients, and in 50% (10/20) of Juvenile AS patients.

Conclusion: Patients with SpA are prevalent in Northwestern Nigeria, and AS predominates. There is significant delay in diagnosing cases of SpA and presence of HLA-B27 was noted in significant proportion in patients with AS and Juvenile AS.

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Spondyloarthritis and autoimmune diseases: preliminary study of 23 Senegalese cases

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Abstract

Background: Spondyloarthrites (SpA) are "mixed-pattern diseases", ranked in between autoimmune and auto inflammatory diseases. It counts seven heterogeneous diseases which share similar physiological, clinical, radiological and genetic (HLA B27) characteristics. Its association with an autoimmune disease is rare.

Objective: To describe its epidemiological and clinical features, as well as evolution under treatment.

Patients and method: This was a descriptive analytic prospective and retrospective study done within a period of 6 years (January 2014- December 2021) in the Rheumatology Department of University Hospital Aristide le Dantec in Dakar, Senegal. These patients were followed as either out-patients or in-patients. Diagnoses were retained on epidemiological, clinical, para clinical arguments in accordance with ASAS (Assessment of Spondyloarthritis international Society) 2009 criteria for spondyloarthritis and usual criteria for each autoimmune disease associated. Data was collected and analyzed for each patient.

Results: Twenty three cases of SpA were found associated to one or more autoimmune diseases. Mean age of our patients was 45.21 years, with extremes (15 and 82 years). Eighteen (76.26%) of these patients were females. Mean diagnostic delay of this association was 80 months (2 – 360 months). The SpA most found associated to autoimmune diseases was ankylosing spondylitis in 20 (86.95%) cases, 2 (8.69%) cses of juvenile spondyloarthritis, and one case of inflammatory bowel diseases associated SpA (4.35%). HLA B27 antigen was requested in 16 cases and was found in 56.25%. Just one autoimmune was found in 20 (86.95%) cases amongst which Sjögren's syndrome was most common in 13 (56.52 %) cases. Two autoimmune diseases were found in two (8.69%) cases one case associating ankylosing spondylitis, Systemic Lupus (LS) and Sjogren's syndrome and one case associating ankylosing spondylitis, Sjogren's syndrome and vitiligo. One case of multiple autoimmune syndrome associated to SpA was found (ankylosing spondylitis, systemic lupus and rheumatoid arthritis). Sjogren's syndrome was the autoimmune disease found to be most associated to SpA in 19 (82.61%) cases. Other autoimmune diseases found were rheumatoid arthritis, systemic lupus, antisynthetase syndrome and vitiligo. Extra articular manifestations were present in 91.30%. Under treatment with classic DMARDs (methotrexate in 65.22%) and evolution was favorable in all cases.

Conclusions: SpA and autoimmune association is rare. It is most frequent in women (76.26%) and the association ankylosing spondylitis and Sjogren's syndrome is dominant (56.52 %) which is in accordance to what is found in literature review. Rheumatologists should think and search more for this rare association for better management of patients.

Key words: Spondyloarthritis, Autoimmune diseases, Africa, Senegal

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Tuberculosis remains a major burden in systemic lupus erythematosus patients in Durban, South Africa

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Abstract

Background: Infections are common in Systemic Lupus Erythematosus (SLE), with tuberculosis (TB) being important in an endemic environment. We studied the prevalence and spectrum of TB in SLE in Durban, South Africa.
Setting: Hospital based study.
Methods: A retrospective record review of SLE patients seen over a 13-year period, and the demographic data, clinical manifestations, laboratory findings, treatment and outcome were noted.
Results: There were 512 SLE patients and 72 (14.1%) had TB. Thirty (41.7%) had Pulmonary TB (PTB) and 42 (58.3%) had Extra-Pulmonary TB (EPTB).The prevalence of TB among the different ethnic groups was 36/282 (12.8%) for Indians, 29/184 (15.8%) African Blacks, 7/26 (26.9%) mixed ethnicity and none among the 18 Whites. Comparison of the 72 SLE-TB patients with 72 SLE controls showed no difference in gender, age at SLE diagnosis and disease duration. The SLE-TB patients had a significant increase in disease activity, arthritis, mucocutaneous lesions, renal involvement, vasculitis, low complement, raised ds-DNA antibodies and cumulative prednisone use over the preceding three months. On multivariate analysis, the only independent risk factor for TB was arthritis (p=0.030).Compared to PTB, the EPTB patients were significantly younger, developed TB earlier after SLE diagnosis, and had higher disease activity. They had increased renal, involvement, thrombocytopaenia, ds–DNA antibodies, and ever use of intravenous methyl prednisolone (IV-MP) and mycophenolate mofetil (MMF). On multivariate analysis, the independent risk factors for EPTB were ever use of MMF (p=0.003) and IV-MP (p=0.027). Analysis of the cumulative SLE criteria showed renal involvement was an independent risk factor for EPTB. The outcome was similar in both groups.
Conclusion: We show an increased TB prevalence (14.1%) in SLE in an endemic area, report increased EPTB (58.3%), identified renal involvement (as a cumulative criterion) as an independent risk factor for EPTB, and confirm the reported association with immunosuppressive therapy

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Coexistence between Von Willebrand disease and systemic lupus erythematosus: a case report

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Abstract

Background: von Willebrand disease is a bleeding disorder characterized by bruises and mucosal bleeding. Although the inherited form is well known, the Acquired Von Willebrand Syndrome (AVWS) is very rare and has been reported with few different diseases. Its coexistence with autoimmune diseases including Systemic Lupus Erythematosus (SLE) represents only 2%.

Case presentation: This was a case of SLE, his condition was preceded with bleeding tendency diagnosed as VWD at the time, when he was a child. He was aged 21 years at the time he presented with bilateral ankle pain and swelling, itchy skin rash and facial butterfly rash. He had past history of recurrent episodes of epistaxis at childhood. Blood tests revealed normocytic normochromic anaemia, normal platelet count with prolonged bleeding time and partial thromboplastin time. After excluding family history of bleeding tendency the diagnosis of AVWS was given when he was a child. Positive ANA antibodies were detected by indirect immunofluorescence showing fine speckled pattern. The diagnosis of SLE was made at adulthood, prednisolone and mycophenolatemofetil were prescribed.

Conclusion: The coexistence and the precedence-observed in our case- of VWD to SLE draw the attention to AVWS and hence the presence of a secondary disease like SLE.

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Work productivity and activity impairment in rheumatoid arthritis patients attending a clinic in Nairobi, Kenya

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Abstract

Background: Rheumatoid Arthritis (RA) is a chronic progressive autoimmune disease that directly impacts productivity and functional status. Despite advances in early diagnosis and therapeutics, RA patients have high rates of early retirement and work absenteeism and are more likely to be unemployed or with reduced earning potential.

Objective: To characterize work disability and work incapacity in rheumatoid arthritis patients attending a rheumatology clinic in Nairobi, Kenya.

Methods: The study included consecutively 100 patients with RA (2010 ACR/EULAR) aged above 18 years and diagnosed with rheumatoid arthritis for at least one year. The sociodemographic and occupational variables were collected, and the Work Productivity and Activity Impairment Questionnaire-General Health (WPAI-GH) was applied to all patients currently employed.

Results: One hundred patients were evaluated, 70% were women with an average age of 43.1 years. Two patients missed work due to RA, with mean absenteeism of 30.64%, presenting an average loss of 19 work hours wasted weekly. In addition, 49% of patients presented some degree of work impairment. Among those with and without work impairment, the average percentage of presenteeism or reduced work performance was 62%. Impairment of Daily Life Activities (DLA) outside work was 49%.

Conclusion: RA patients have reduced productivity at work and performing daily life activities. There is a need to introduce workplace productivity assessment in routine evaluation in patients with rheumatoid arthritis and more studies to look into the determinants of reduced productivity amongst RA patients.

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Clinico-epidemiological pattern of rheumatic diseases seen in a tertiary hospital in Southern Nigeria

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Abstract

Background: Rheumatic diseases are amongst the most common disease which cause disability and reduces the quality of life of those affected. However, paucity of reports on the spectrum of these diseases in southern Nigeria has resulted in low awareness and poor management of these patients.
Objective: This study aimed to determine the clinico-epidemiological pattern of rheumatic diseases in University of Benin Teaching Hospital, Nigeria (after the establishment of the Rheumatology unit in 2017). This will enable better understanding of the disease and improve the quality of healthcare provided to the patients.
Setting: Hospital based study.
Methods: This was a descriptive retrospective study of patients seen over 5 years from August 2017 to August 2022. All patients had their profiles extracted from medical records. The Data obtained was analysed using SPSS Version 21.
Results: They were 805 patients registered in the medical records, of which some patients had multiple rheumatic conditions,thus the total number of rheumatic diseases diagnosed was 961, ratio 1.2:1 They were predominantly female 619 (76.99%), average age of 54+17.9 years. In decreasing order of occurrence,the most prevalent rheumatic disease was degenerative arthritis (n=597, 74.16%) followed by inflammatory arthritis (n=136, 16.8%) and autoimmune rheumatic diseases (n=123,15.28%), while the least seen was Infective arthritis (n=2,0.25%).
Conclusion: Rheumatic diseases are common in Southern Nigeria with patients presenting with multiple diagnosis. Osteoarthritis was seen in the majority of patients, While rheumatoid arthritis and systemic lupus erythematosus were the commonest amongst the inflammatory and autoimmune group. The female preponderance in these conditions was also noted as earlier stated in literature. Prompt recognition and management of these diseases will result in better outcome.

Key words. Rheumatic disease, Osteoarthritis, Rheumatoid arthritis, Systemic lupus erythematosus

Understanding mental health in patients with axial spondyloarthritis in South Africa: Results from the International Map of Axial Spondyloarthritis (IMAS)

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Abstract

Background: Axial spondyloarthritis (axSpA) is a chronic disease that affects the patients' mental health.

Objective: To assess the prevalence of poor mental health and associated factors in South African patients with axial spondyloarthritis.

Methods: Data from 146 South African patients participating in the International Map of Axial Spondyloarthritis (IMAS) study through an online survey were analysed. Mental health was assessed using the 12-item General Health Questionnaire (GHQ-12). The sample was divided into two groups: 1) Patients with <3 GHQ-12 scale points (good mental health); 2) Patients with ≥3 GHQ-12 scale points (poor mental health). Mann-Whitney and Pearson's chi-squared tests were used to analyse relationships between mental health and sociodemographic factors, lifestyles, patient-reported outcomes, treatment and working impact. Univariable and multivariable linear regression were used to identify variables that could explain poor mental health.

Results: One hundred and forty six South African patients were evaluated, mean age of 44.7 years, 82.2% were women, and 67.8% married. The mean of GHQ-12 was 5.3 (±3.8) and 69.9% had poor mental health (Table 1). Compared to good mental health, patients with poor mental health were more frequently younger (43.5 vs 47.5, p=0.042), with higher disease activity (6.3 vs 5.3, p=0.001), with work-related issues (67.1% vs 32.9%, p=0.033), and difficulty in finding a job (78.8% vs 21.2%, p=0.002; Table 2). In univariable logistic regression analyses, the factors associated with poor mental health were younger age (OR= 0.962), higher disease activity (OR= 1.424) and difficulties in finding a job (OR= 3.722). In multivariable logistic regression, the factors explaining poor mental health were higher disease activity (OR= 1.316) and difficulty in finding a job (OR= 2.663; Table 3).

Conclusion: More than two-thirds of axSpA patients experience poor mental health in South Africa. Furthermore, poor mental health was present in patients with higher disease activity and in patient with difficulty in finding a job. Healthcare professionals should pay close attention to patients with high disease activity and treat them internally or refer them to specialized services, as this could also directly affect their work situation.

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Table 1: Sociodemographic, lifestyles, PROs, diagnosis, comorbidities and treatment of the sample (N=146, unless specify)

		Mean±SDorn (%)
Sociodemographic		
Age		44.7±10.3
Gender	Male	26(17.8)
	Female	120(82.2)
Education level	High school	42(28.8)
	College	50(34.2)
	Graduate	54(37.0)
Marital status, n=143	Single	24(16.8)
	Married	97(67.8)
	Divorced/separated	20(14.0)
	Widow	2(1.4)
Employment status, n=120	Employed	81(67.5)
	Employed–fulltime	3(2.5)
	Self employed	19(15.8)
	Unemployed	3(2.5)
	Early retirement	2(1.7)
	Homemaker	7(5.8)
	Student	5(4.2)
Member of patient organizations	Yes	125(85.6)
	No	21(14.4)
Lifestyles		
BMI	Underweight/normal weight	52(35.6)
	Overweight/obesity	94(64.4)
Smoking	Yes	29(19.9)
	No	117(80.1)
Alcohol	Yes	45(30.8)
	No	101(69.2)
Physical activity, n=145	Yes	115(79.3)
	No	30(20.7)
Patient Reported-Outcomes (PROs)		
BASDAI(0-10)		6.0±1.8
BASDAI cut-off(≥4)		127(87.0)
GHQ-12		5.3±3.8
GHQ-12(≥3). Poor mental health		102(69.9)
Functional limitation(0-54)		19.1±13.1
Spinal stiffness(3-12)		8.6±1.8
Number of physical comorbidities		3.1±2.3
Treatment		
Used NSAID, n=144	Yes	136(94.4)
	No	8(5.6)
Used DMARDs, n=140	Yes	111(79.3)
	No	29(20.7)
Used Biologics	Yes	62(42.5)

Table 2: Associations between sociodemographic, lifestyle, patient reported outcomes, treatment, working impact and mental health (N= 146, unless specify)

		Mean±SDorn(%) GHQ-12		P-value
		<3	≥3	
		44(30.1%)	102(69.9%)	
Sociodemographic				
Age		47.5±10.4	43.5±10.1	0.042
Gender	Male	8(30.8)	18(69.2)	0.938
	Female	36(30.0)	84(70.0)	
Education level	High school	11(26.2)	31(73.8)	
	College	13(26.0)	37(74.0)	0.379
	Graduate	20(37.0)	34(63.0)	
Maritalstatus	Single	5(20.8)	19(79.2)	
	Married	31(32.0)	66(68.0)	0.639
	Divorced/separated	7(35.0)	13(65.0)	
	Widow	1(50.0)	1(50.0)	
Employment status, n=120	Employed	29(35.8)	52(64.2)	
	Employed–fulltime	0(0.0)	3(100.0)	
	Self employed	2(10.5)	17(89.5)	
	Unemployed	1(33.3)	2(66.7)	0.166
	Early retirement	0(0.0)	2(100.0)	
	Homemaker	4(57.1)	3(42.9)	
	Student	2(40.0)	3(60.0)	
Member of patient organizations	Yes	37(29.6)	88(70.4)	0.730
	No	7(33.3)	14(66.7)	
Lifestyle				
BMI	Underweight/normal weight	15(28.8)	37(71.2)	0.800
	Overweight/obesity	29(30.9)	65(69.1)	
Smoking	Yes	13(44.8)	16(55.2)	0.054
	No	31(26.5)	86(73.5)	
Alcohol	Yes	17(37.8)	28(62.2)	0.179
	No	27(26.7)	74(73.3)	
Physical activity, n=145	Yes	38(33.0)	77(67.0)	0.080
	No	5(16.7)	25(83.3)	
Patient Reported-Outcomes (PROs)				
BASDAI(0-10)		5.3±1.7	6.3±1.7	0.001
Functional Limitation(0-54)		15.9±12.1	20.5±13.3	0.059
Spinal Stiffness(3-12)		8.2±1.7	8.7±1.9	0.065
Number of physical comorbidities		3.1±2.3	3.1±2.3	0.828
Treatment				
Used NSAIDs, n=144	Yes	38(27.9)	98(72.1)	0.182
	No	4(50.0)	4(50.0)	
Used DMARDs, n=140	Yes	36(32.4)	75(67.6)	0.389
	No	7(24.1)	22(75.9)	
Used Biologics	Yes	21(33.9)	41(66.1)	0.398
	No	23(27.4)	61(72.6)	
Working impact due to axSpA				
Work related issues, n=81	Yes	25(32.9)	51(67.1)	**0.033**
	No	4(80.0)	1(20.0)	
Difficulty finding a job, n=131	Yes	18(21.2)	67(78.8)	**0.002**
	No	23(50.0)	23(50.0)	
Work choice determined by axSpA, n=133	Yes	14(30.4)	32(69.6)	0.468
	No	28(32.2)	59(67.8)	
	No	38(37.3)	64(62.7)	

Table 3: Regression analysis for variables explaining the risk of mental health (N=146)

	Univariable logistic regression		Multivariable logistic regression	
	OR	95%CI	OR	95%CI
Age	0.962	**0.928,0.997**	0.963	0.924,1.004
BASDAI(0-10)	1.424	**1.148,1.766**	1.316	**1.020,1.698**
Work related issues. Yes	8.160	0.866,78.876	-	-
Difficulty finding a job. Yes	3.722	**1.710,8.101**	2.663	**1.136,6.245**

Assessing diagnostic delay in axial spondyloarthritisin South Africa: Results from the International Map of Axial Spondyloarthritis (IMAS)

Makan K[1], Garrido-Cumbrera M[2,3], Tarr G[4], Correa-Fernández J[2], Van Dam M[5]

Abstract

Background: Axial spondyloarthritis (axSpA) is associated with a significant diagnostic delay, impacting the health of patients.

Objective: To estimate the diagnostic delay and its associated factors in axSpA patients in South Africa.

Methods: One hundred and forty six South African patients participating in the International Map of Axial Spondyloarthritis (IMAS) study through an online survey (October-December 2021), were analysed. Diagnostic delay was calculated as the difference between age at diagnosis and age at symptom onset reported by participants. Since diagnostic delay may present outliers, the median was used as the central position statistic and the cut-off point was set at 7, dividing the sample into two groups: 1) Patients with < 7 years of diagnostic delay; 2) Patients with ≥ 7 years of diagnostic delay. Univariable and multi-variable linear regression were used to identify variables associated with diagnostic delay.

Results: The mean age was 44.7 years and 82.2% were women. The average diagnostic delay was 10.8 years and the median was 7.0 (Table 1). Patients with higher diagnostic delay (≥7) presented higher number of Health Care Professionals (HCPs) seen before diagnosis (3.9 vs. 3.0, p=0.021) and younger onset of symptoms (20.5 vs. 33.1, p<0.001; Table 2). Univariable logistic regression analyses confirmed higher number of HCPs visits before diagnosis (OR= 1.203) and younger age at symptoms onset (OR= 0.873) were associated with a longer diagnostic delay, however on multivariate regression analysis, only younger age at symptoms onset remained significant (OR= 0.873; Table 3).

Conclusion: Diagnostic delay in South Africa is considerably higher than in other IMAS countries (10.8 vs. 7.4 in the European countries of IMAS). This delay was longer in patients with younger age at symptom onset and those with higher HCPs seen prior to diagnosis. These results suggest a need to increase awareness of axSpA to facilitate earlier intervention and better patient outcomes.

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Table 1: Sociodemographic, lifestyles, PROs, diagnosis, comorbidities, and treatment of the sample (N=146, unless specify)

		Mean±SDorn (%)
Socio-demographic		
Age		44.7±10.3
Gender	Male	26 (17.8)
	Female	120(82.2)
Education level	High school	42 (28.8)
	College	50 (34.2)
	Graduate	54 (37.0)
Marital status, n=143	Single	24 (16.8)
	Married	97 (67.8)
	Divorced/separated	20 (14.0)
	Widow	2(1.4)
Employment status, n=120	Employed	81 (67.5)
	Employed–fulltime	3(2.5)
	Self employed	19 (15.8)
	Unemployed	3(2.5)
	Early retirement	2(1.7)
	Homemaker	7(5.8)
	Student	5(4.2)
Member of patient organizations	Yes	125(85.6)
	No	21 (14.4)
Lifestyles		
BMI	Underweight/normal weight	52 (35.6)
	Overweight/obesity	94 (64.4)
Smoking	Yes	29 (19.9)
	No	117(80.1)
Alcohol	Yes	45 (30.8)
	No	101(69.2)
Physical activity, n=145	Yes	115(79.3)
	No	30 (20.7)
Patient reported-outcomes		
BASDAI(0-10)		6.0±1.8
BASDAI cut-off(≥4)		127(87.0)
GHQ-12		5.3±3.8
GHQ-12(≥3)		102(69.9)
Functional Limitation(0-54)		19.1±13.1
Spinal Stiffness(3-12)		8.6±1.8
Diagnosis		
Age at symptom onset		26.7±11.4
Age at diagnosis		37.5±10.8
Diagnostic delay		10.8±10.6
HCP that made the diagnosis, n= 131	Rheumatologist	102(77.9)
	GP	18 (13.7)
	Orthopaedic specialist	11 (8.4)
Number of HCPs seen before diagnosis		3.4±2.2
Number of test performed before diagnosis		6.1±6.1
HLA-B27, n=11 5	Positive	83 (72.2)

	Negative	32 (27.8)
Comorbidities		
Anxiety, n=140	Yes	68 (48.6)
	No	72 (51.4)
Depression, n=142	Yes	76 (53.5)
	No	66 (46.5)
Sleep disorders, n=140	Yes	74 (52.9)
	No	66 (47.1)
Used NSAID, n=144	Yes	136(94.4)
	No	8(5.6)
Used DMARDs, n=140	Yes	111(79.3)
	No	29 (20.7)
Used Biologics	Yes	62 (42.5)
	No	84 (57.5)

Table 2: Associations between sociodemographic and disease-related variables and diagnostic delay (N= 146, unless specify)

		Mean±SDorn(%) Diagnostic Delay		
		<7 years	≥7 years	P-value
Sociodemographic				
Gender	Male	15 (57.7)	11 (42.3)	0.346
	Female	57 (47.5)	63 (52.5)	
Education level	High school	26 (61.9)	16 (38.1)	
	College	19 (38.0)	31 (62.0)	0.073
	Graduate	27 (50.0)	27 (50.0)	
Marital status	Single	14 (58.3)	10 (41.7)	
	Married	45 (46.4)	52 (53.6)	0.265
	Divorced/separated	12 (60.0)	8(40.0)	
	Widow	0(0.0)	2(100.0)	
Employment status, n=256	Employed	41 (50.6)	40 (49.4)	
	Employed–fulltime	1(33.3)	2(66.7)	
	Self employed	10 (52.6)	9(47.4)	0.382
	Unemployed	1(33.3)	2(66.7)	
	Early retirement	2(100.0)	0(0.0)	
	Homemaker	1(14.3)	6(85.7)	
	Student	2(40.0)	3(60.0)	
Member of patient organizations	Yes	58 (46.4)	67 (53.6)	0.086
	No	14 (66.7)	7(33.3)	
BMI	Underweight/normal weight	20 (38.5)	32 (61.5)	0.051
	Overweight/obesity	52 (55.3)	42 (44.7)	
Smoking	Yes	13 (44.8)	16 (55.2)	0.589
	No	59 (50.4)	58 (49.6)	
Alcohol	Yes	21 (46.7)	24 (53.3)	0.669
	No	51 (50.5)	50 (49.5)	
Physical activity, n=145	Yes	57 (49.6)	58 (50.4)	0.777
	No	14 (46.7)	16 (53.3)	

Patient Reported-Outcomes				
BASDAI(0-10)		6.3±1.7	5.7±1.8	0.089
GHQ-12		5.8±3.8	4.7±3.8	0.070
Functional simitation(0-54)		18.1±12.6	20.2±13.6	0.375
spinal Stiffness(3-12)		8.4±2.0	8.7±1.5	0.426
Diagnosis				
Age at symptom onset		33.1±11.0	20.5±7.9	<0.001
Diagnosed by rheumatologist, n=131	Yes	48 (47.1)	54 (52.9)	0.406
	No	24 (54.5)	20 (45.5)	
Number of HCPs seen before diagnosis		3.0±2.0	3.9±2.4	0.021
Number of test performed before diagnosis		6.0±5.7	6.2±6.6	0.905
HLA-B27, n= 115	Positive	42 (50.6)	41 (49.4)	0.225
	Negative	18 (56.3)	14 (43.8)	
Comorbidities				
Anxiety, n=140	Yes	38 (51.4)	36 (48.6)	0.605
	No	31 (47.0)	35 (53.0)	
Depression, n=142	Yes	37 (48.7)	39 (51.3)	0.876
	No	33 (50.0)	33 (50.0)	
Sleep disorders, n=140	Yes	34 (40.0)	34 (50.0)	0.870
	No	35 (48.6)	37 (51.4)	
Treatment				
Used NSAIDs, n=144	Yes	69 (50.7)	67 (49.3)	0.367
	No	2(25.0)	6(75.0)	
Used DMARDs, n=140	Yes	55 (49.5)	56 (50.5)	0.992
	No	14 (48.3)	15 (51.7)	
Used Biologics	Yes	25 (40.3)	37 (59.7)	0.062
	No	47 (56.0)	37 (44.0)	

Table 3: Regression analysis for variables explaining the diagnostic delay (N=146)

	Univariable logistic regression		Multivariable logistic regression	
	OR	95% CI	OR	95% CI
Age at symptom onset	0.873	0.833,0.915	0.873	0.833,0.916
Number of HCPs[1] seen before diagnosis	1.203	1.027,1.410	1.144	0.954,1.371

[1]HCP: Healthcare professionals

Relative frequencies and determinants of ACPA and RF among blood donors in the city of Kinshasa

Mbuyi J[1], Mbuyi-Muamba JM[1], Nganga M[1], Nkodila A[2], Malemba JJ[1], Meyer P[1], Lebughe P[1], Mulumba C[1], Mavinga A[1], Matanda D[1]

Abstract

Background: The detection of Anticyclic Citrullinated Peptide Antibodies (ACPA) and Rheumatoid Factor (RF) in healthy subjects often precedes the onset of RA by several years. They are therefore associated with a high risk of developing RA and are controlled by genetic and environmental factors.

Objective: The aim of this study was to determine the prevalence and determinants of ACPA and RF in blood donors in the city of Kinshasa.

Methods: This was a cross-sectional study conducted on blood donors in Kinshasa (DRC) from December 2020 to March 2021 in four blood banks. The variables of interest were; age, sex, education, socioeconomic level, occupation, alcohol consumption, and smoking. RF and ACPA levels were determined by enzyme immunoassay with chemiluminescence. The statistical significance level set was $p \leq 0.05$.

Results: The sample for this study consisted of 267 blood donors, including 235 males and 32 females. The sex ratio M/F was 7.3. The mean age of the donors was 34.6 ± 11.6 years. The prevalence of ACPA was 6%. Low socioeconomic level (ORa 2.52 with 95% CI [1.46-5.01],p=0.01), low educational level (ORa 1.98 with 95% CI [1.42-5.16], p=0.01) and regular alcohol consumption (ORa 2.24 with 95% CI [1.42-3.65],p=0.02) emerged as independent determinants of the presence of ACPA. The prevalence of RF was 5.6%, with no association with the factors sought.

Conclusion: This study showed that regular alcohol consumption, low socio-economic and education levels are determinants of the presence of ACPA, but not of RF. The strong association between the production of ACPA and RA indicates the need for a study on the clinical outcome of asymptomatic ACPA carriers.

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Epidemiological and clinical profile of fibromyalgia in patients attending the University Hospital of Kinshasa

Mavinga A[1], Mbuyi J[1], Matanda D[1], Mulumba C[1], Nkodila A[2], Lebughe P[1], Mbuyi-Muamba JM[1], Malemba JJ[1]

Abstract

Background: Fibromyalgia is a controversial and often under-reported clinical entity in routine medical practice.
Objective: To describe the epidemiological and clinical profile of fibromyalgia in patients attending the University Hospital of Kinshasa (UHK).
Methods: This hospital-based study is a series of clinical cases carried out in patients attending the rheumatology unit of UHK from December 2020 to March 2022. The following informations were collected: age, sex, painful symptomatology, psychosomatic signs, circumstances of the disease onset, factors that emphasize or reduce symptoms, the number of previous medical visits and the impact on socio-professional life. The diagnosis of fibromyalgia was defined according to the ACR 2010 criteria. Fibromyalgia was considered severe when it was associated with disability. Standard statistical tests were used to analyze the results.

Results: Five hundred and eighty five patients were received during the study period. The diagnosis of fibromyalgia was retained in 63 of them (10.8%). The M/F sex ratio was 0,5 and the average age was 50.9±12.4 years. The average diagnostic score was 17.6±3.6. Painful manifestations were dominated by arm involvement (84.1%). Fatigue and anxiety were observed in 59 (93.7%) and 26 (41.3%) patients respectively. The average number of previous medical visits number was 5.2±1.6. Fibromyalgia was triggered by emotional stress in 28 (44.4%) patients and quiet rest (42.9%) was the calming factor in 27 (42,9%) patients. Thirty eight patients (60.3%) developed the severe form of the disease.
Conclusion: Fibromyalgia is among common diseases which patients visit the rheumatology unit. So, it is requires a special consideration from health care workers particularly rheumatologists for an early diagnosis.

Key words: Fibromyalgia, Epidemiological and clinical profile, Kinshasa

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The Rhupus syndrome: case report

Juma P[1], Karanja R[2], Simani P[3]

Abstract

Background: We present a case of the Rhupus syndrome which is a rare clinical entity with features of both Rheumatoid Arthritis (RA) and Systemic Lupus Erythematosus (SLE). Rhupus patients also have several distinct clinical features and there is still a debate as to whether it is an overlap syndrome or a distinct clinical condition.

Case report: This was a case of a 38-year-old African female who presented with pain and swelling involving the small joints in her hands, wrists, knees and ankles. She had been diagnosed with Juvenile Rheumatoid Arthritis (JRA) at the age of 6 years and was followed up for 26 years for this. At presentation to the clinic she fulfilled the EULAR criteria for RA. Subsequently at the age of 32 years she developed features of SLE. She had a malar rash, photosensitivity, swellings on her earlobes, generalized tonic clonic seizures and proteinuria. She fulfilled the EULAR criteria for SLE at this time and was successfully treated with a DMARD regimen.

Conclusion: Our report presents further evidence of the co-existence of SLE and RA in an African female. Further research needs to be conducted to determine the epidemiology and clinical features of this syndrome in an African population.

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Undifferentiated connective tissue disorder: a descriptive study in a rheumatology clinic

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Abstract

Background: Undifferentiated Connective Tissue Disorder (UCTD) is a condition encountered in clinical practice presenting with features of an autoimmune disorder but not fulfilling criteria of a Connective Tissue Disease (CTD).

Objective: The aim of this study was to describe the history and clinical features of patients with UCTD attending a rheumatology clinic.

Methods: All medical records of patients registered in the rheumatology clinic in the ten years between 2012 and 2022 as presenting with CTD were reviewed. Patients fulfilling a criteria for a defined disease were excluded. Also excluded were patients with diabetes, thyroid disorders, autoimmune hepatic disorders and colitis. Twenty three patients were recruited into the study. The history and clinical features were documented on a questionnaire and analysed for descriptive statistics using a standard statistical package (STATA Version 16.1)

Results: Two thousand three hundred and seventy five patients reported to our rheumatology clinic in the period 2012 to 2022. Of these 217 patients had CTD. Twenty three (11%) were recruited with UCTD. Twenty (87%) were females, hence a male to female ratio of 1:7. The age range was 23 years to 48 years with a mean age of 37 years. Eleven (48%) of patients had a family history of CTD in a first degree relative, while a history of diabetes was recorded in 7(30%) of patients families. Arthritis and fatigue were the most common clinical presentation (100%) and (96%) respectively. Sicca symptoms were noted in 12(52%) of patients. Anaemia was noted in 8(35%) while leukopenia was noted in 6(26%) of patients and serositis in 4(17%). All patients were ANA positive with the speckled fluorescent pattern being the single most common when reported. SSA antibodies were recorded in 9(39%) of patients.

Conclusion: African patients with UCTD present a pattern of disease similar to that observed elsewhere.

A rational approach to the diagnosis of lupus myocarditis

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Abstract

Up to 10% of patients with Systemic Lupus Erythematosus (SLE) develop clinically evident Lupus Myocarditis (LM). The clinical presentation of LM varies from a resting tachycardia to fulminant Congestive Cardiac Failure (CCF) and even mortality. In the absence of a single diagnostic test, a rational and practical diagnostic approach in patients with suspected LM is essential. Troponin-I and creatinine kinase (as markers of myocyte injury) are not always elevated and has a poor negative predictive value for LM. Although an electrocardiogram is essential to exclude other causes of CCF such as acute coronary syndrome or conduction disorders, abnormalities in the setting of LM are non-specific. Various echo cardiographic modalities (segmental wall motion analyses and speckle tracking echocardiography) may be indicative of regional and/or global left ventricular dysfunction and is known to be more sensitive than conventional echocardiography, especially in early LM. The current non-invasive diagnostic modality of choice in myocarditis (all types) is Cardiac Magnetic Resonance imaging (CMR). Although more sensitive and specific than echocardiography, CMR may be limited in the context of SLE due to technical challenges (unstable and uncooperative patients), contra-indications to gadolinium use (acute kidney injury, lupus nephritis) and limited literature regarding the application of recommended diagnostic CMR criteria in SLE. Subclinical myocardial dysfunction and/or injury may be detected by both echocardiography and CMR. The clinical significance of these findings however remains uncertain. A multidisciplinary decision-making approach, interpreting diagnostic test results within the clinical context of the patient is essential to ensure an accurate, early diagnosis of LM.

Remission of RA in Africa – reality or pipedream?

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Abstract

The main factors influencing positive outcome are related to early diagnosis, early initiation of Disease Modifying Anti-Rheumatic Drugs (DMARDs), access to health care and medication, availability of competent health care providers and facilities for monitoring response. The 2010 criteria for the diagnosis of RA have come a long way in improving early diagnosis, even in the absence of serology. However, studies from sub-Saharan Africa show that in most centres, up to 2010, late diagnosis, deformities and disability were present in the majority of patients at presentation. Many of these patients would no longer benefit from DMARD therapy since the mean disease duration varied from 3 to 9 years in these studies. RA treatment is aimed at relieving pain, reducing joint inflammation, prevent joint destruction, restore function to disabled joints, correct deformed joints and, ultimately, improve the quality of life of our patients. Inflammation in RA is driven by an imbalance between pro-inflammatory and anti-inflammatory cytokines. While prednisone, which is used extensively for RA across Africa, is a powerful anti-inflammatory drug it does not prevent progression of damage to the articular cartilage. The cytokine milieu is best controlled by conventional and biologic DAMRDs. Conventional DMARDs can effectively control RA if started early in the course of the disease sometimes as combination therapy. If these fail, one would need to resort to biologic DMARDs, which are selectively targeted monoclonal antibodies against specific cytokines. There are several now available and are directed at cytokines and mediators at different aspects of the inflammatory pathway. While biological DMARDs are not readily available across all countries in Africa, conventional DMARDs, if initiated early, can certainly increase the number of RA patients achieving remission, even in Africa. Remission is now a reality rather than a pipe dream in Africa.

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