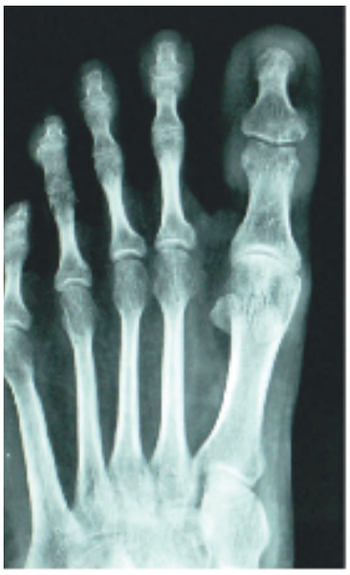

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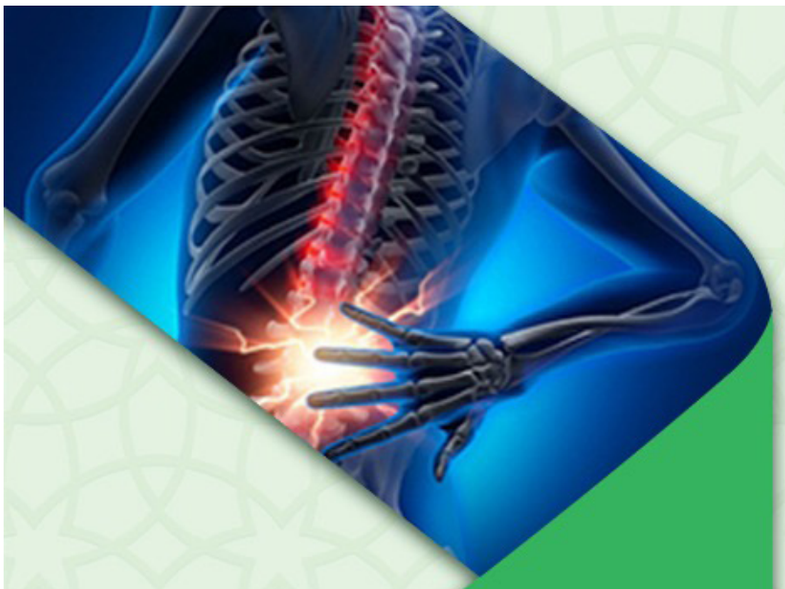

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Editorial

Digital technology: The key to unlock rheumatology in Africa

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Musculoskeletal (MSK) conditions are the highest contributors to disability worldwide[1], with a third of the global population having to live with MSK pain. This leads in turn to mental ill health, loss of work and reduced ability to engage in social roles[1]. There has been a historic underestimation of the prevalence of MSK disorders in sub-Saharan Africa, but in fact the burden of this conditions is up to 2.5 times of that found in developed countries[2,3]. Whilst degenerative diseases are frequently seen[4], a significant proportion of MSK disease is inflammatory, such as Rheumatoid Arthritis (RA), where prompt and appropriate treatment can prevent disability.

The prevalence of RA in Africa was recently estimated to be 0.42%, affecting 4.3 million people[5]. However, because of wide-spread under diagnosis, the true figure is likely to be considerably higher[5] and those patients who are diagnosed, are often treated sub-optimally with long and high doses of steroids, inadequate doses of disease modifying therapy and no access to biologic therapy[6]. Consequently, many live with high levels of disability and subsequent comorbidities that are potentially preventable[7].

There are significant challenges to the provision of rheumatology healthcare in Africa. Accessing even basic healthcare is difficult in some parts of Africa, especially in rural communities and the lack of accurate data on disease prevalence makes governmental resource planning near impossible. Patients often travel long distances on poor transport infrastructure to consult with a general physician - let alone a specialist - and access investigations and medications. Such journeys are frequently impossible, as many patients are unable to leave their livelihoods for even short periods or afford the travel[8]. Limited rheumatology training means there are few, if any, rheumatologists in most sub-Saharan African countries. Indeed, less than 150 rheumatologists currently serve 1 billion people in sub-Saharan Africa, considerably less than the WHO recommended ratio of one per 100,000 population[9]. Consequently, most patients are looked after by general physicians or even orthopaedic surgeons who are not equipped to prevent joint failure. A widespread lack of awareness of rheumatological conditions within the public and general physicians adds to these problems, with patients typically visiting local healers first and presenting to physicians late or not at all[8]. The average time to RA diagnosis in a private clinic in Lagos, Nigeria was reported as 63 months[10]. For those patients who do receive specialist care, there remains difficulties with patient education due to literacy rates, regional languages, the use of traditional medicines and cultural beliefs[8]. In addition, disease modifying therapies require regular blood monitoring which is not always practical in a low resource setting and biologic drugs come at a high cost, with significant risks of infection.

We believe digital technology could provide a critical tool to overcome the challenges faced in delivering rheumatology healthcare in Africa. The face of international research and training has already changed with advances in technology such as global web-based data sets and the development of effective e-Learning. Now, with the emergence of COVID-19 and the need to reduce face to face patient interaction, virtual patient care is set to become the new "norm".

The WHO has identified digital technologies as a vital resource to improve access to healthcare in Africa[11] and has developed an e-Health toolkit that sets out strategies for governments to implement e-Health[12]. There are already good examples of e-Health projects aimed at a wide range of specialists, community doctors and allied health professionals, which could easily be transferable to rheumatology. The digital infrastructure is increasingly available to support this strategy. Whilst currently only 57% of the population is over 14 years old[13], as the fastest growing region, it is estimated that half of the population in sub-Saharan Africa will subscribe to mobile services by 2025 and 40% will have access to the internet[14]. Of those, the percentage who use smartphones and therefore can use "apps"

will grow from 39% in 2018 to 66% in 2025[14]. The benefit of mobile technologies lies in access. Barriers such as large geographical distance, high cost, ability to disseminate information and difficulties in adapting to local contexts can easily be overcome by virtual patient care[15].

There is also a need for enhanced rheumatology specialist training in Africa. eLearning courses such as the EULAR online course have been successfully used to help train rheumatologists in Kenya, but the development of more Africa-specific and clinically relevant e-Learning would increase accessibility for trainees across the region. This year, in light of COVID-19, the annual EULAR congress is being delivered online. Although it remains to be seen how successful this will be, it represents an exciting opportunity for clinicians in Africa to attend international conferences and engage with the wider scientific community without the huge cost burden.

Telemedicine overcomes the geographical divide between patients and clinicians. Babyl, affiliated with Babylon health, provides video consultations to patients in Rwanda[16]. It has grown exponentially and in 2018 the Government of Rwanda, in partnership with the Bill and Melinda Gates Foundation, announced that they will give access to Babyl to the entire population. Similar applications have the potential to enable patients in rural areas to speak to specialist rheumatologists. Technology can also help provide specialist support to local general clinicians or allied health professionals. In Ghana, the Novartis Foundation and its partners have developed a system which connects frontline health workers to consultation centers in referral hospitals several hours away[17]. This has been so successful that it is being scaled up nationally. Virtual doctors, a UK based charity, links clinical officers in rural Zambia and Malawi with doctors in the UK who provide advice and education on individual cases[18]. Although not developed in the rheumatology community yet, there may be scope for international online multi-disciplinary meetings to discuss complex cases using video platforms. All these technologies mean that, even with low numbers of rheumatology specialists, their expertise can reach more patients.

Accessing and monitoring disease modifying therapy and biologics also presents a huge challenge. These specialist medications are often not included on the "national formulary" and are expensive to source from abroad[19]. Patients can travel long distances, only to find that the medicines they need are not in stock. In Uganda this has been overcome by the use of a system into which 27,000 government health workers report on medicine stock around the country[20]. In Ghana and Rwanda, "Zipline" uses drones to deliver blood and medications to remote clinics, ordered by an SMS or WhatsApp message[21]. Although still in their infancy, these initiatives are particularly promising for use in rheumatology as they allow individualised medication requests. Management of chronic conditions such as RA require patient engagement, long term follow up and regular blood monitoring. WhatsApp, the most popular social app in Africa is widely available and a useful tool to share information, even with people who are illiterate by the use of audio notes. Rheumatologists in Senegal already use WhatsApp to communicate blood test results with their patients and the application was used by the British Broadcasting Corporation (BBC) in the Ebola crisis to share information with people in rural and quarantined areas[22]. Patient initiated follow up and symptom tracker applications have already been developed, allowing patients and clinicians to monitor and identify disease flares in a timely way and prevent the need for unnecessary consultations.

The true success of digital technology in supporting rheumatology care will depend on all elements of e-Health working together. There are potential problems of unclear healthcare system responsibilities, unreliable infrastructure and most of all in-ability to scale up these initiatives to create long-term sustainability. Well trained doctors and allied health professionals are vital to help deliver e-Health projects and, given the huge shortfall of rheumatologists currently, there is a long way to go before adequate manpower is on the ground.

In rheumatology we refer to the advent of biologics as a paradigm shift in the treatment of patients with RA. If implemented correctly, digital technology has the potential to deliver a similar paradigm shift in the provision of rheumatology to Africa and to transform and widen access to rheumatology specialist services.

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Review article

Glucocorticoid use in rheumatology: a review

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Abstract

Background: Glucocorticoids play a pivotal role in the management of many rheumatologic diseases. However, glucocorticoid usage is associated with numerous adverse effects that involves almost all the major organ systems in the body. Hence, there is a need to balance the benefits and risks of glucocorticoids. There is also ongoing research for newer drugs with glucocorticoids actions with no or minimal adverse effects.

Objective: The aim of this literature review is to address the mechanism of action, pattern of use of glucocorticoids in various inflammatory arthritis and the adverse effects of glucocorticoids.

Data source: The literature review uses medical science based literature published locally and internationally on use of glucocorticoids in rheumatological diseases.

Conclusion: Glucocorticoids are very effective in the management of rheumatologic diseases. However, their use is curbed by the occurrence of adverse effects. These adverse effects can be abated if glucocorticoids are used prudently. There is no absolutely safe dose of glucocorticoids, only relatively safer doses. The clinical use of newer glucocorticoid drugs with no adverse effects will not occur in the near future.

Key words: Glucocorticoids, Rheumatology, Mechanism of action, Adverse effects, Pattern of glucocorticoid use, New glucocorticoid formulations

Introduction

Glucocorticoids play an important role in the management of rheumatologic diseases. It was discovered seven decades ago, when Philip Hench reported its dramatic effect on a young lady suffering from severe rheumatoid arthritis[1]. It is the most frequently used anti-inflammatory drugs despite the development of DMARDs and biological agents. However, its use is curbed by occurrence of adverse effects. This article summarizes the current use of corticosteroids in rheumatology.

Mechanism of action

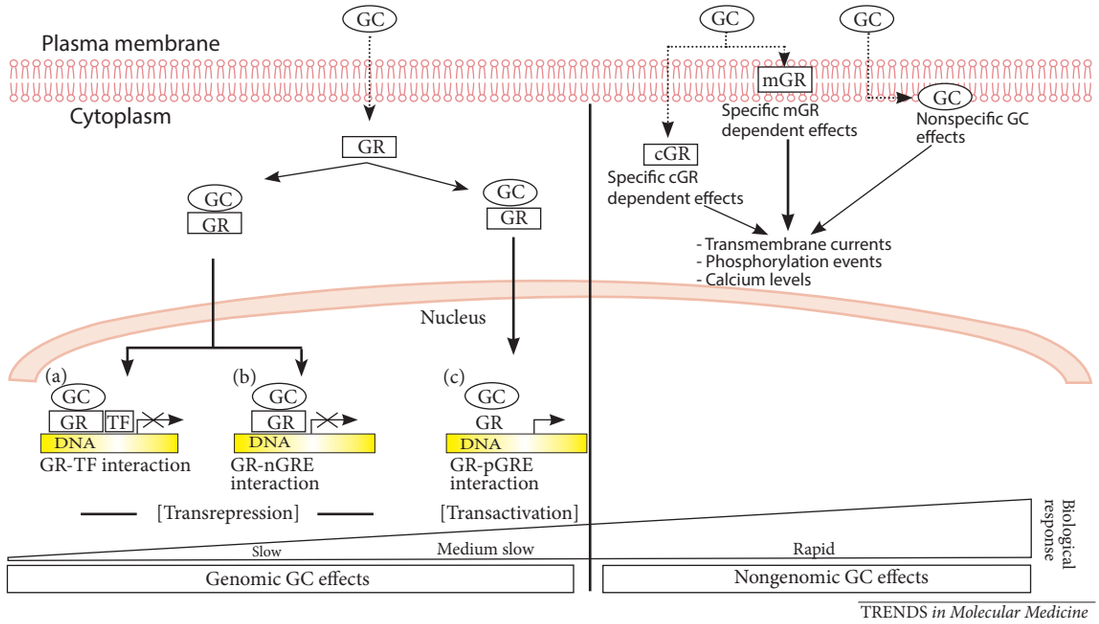
The effects of glucocorticoids are mediated by different mechanisms[2]. Two main mechanisms include the classic genomic and the non-genomic mechanism (Figure 1). The classic genomic mechanism is the most important mechanism of action in low dose therapy while the non-genomic mechanism is important in high dose therapy.

In the classic genomic mechanism, the glucocorticoid molecule enters into the cytoplasm whereby it binds to the cytosolic Glucocorticoid Receptor (GCR). This forms an activated glucocorticoid-GCR complex, which translocate into the nucleus and initiates transactivation and transrepression.

Transactivation occurs when two activated glucocorticoid-GCR complex form a dimer and bind to the glucocorticoid responsive element upregulating regulatory proteins synthesis. These proteins are responsible for the metabolic and some anti-inflammatory effects. In transrepression, the glucocorticoid-GCR complex inhibits transcription of proinflammatory transcription factors like nuclear factor kb. This process down-regulates pro-inflammatory protein synthesis[2].

Genomic processes require about thirty minutes for changes to occur in synthesis of regulatory protein, and takes hours to days for changes to occur at cellular or organ level. It was thought that the anti-inflammatory property of glucocorticoid was due to transrepression while the metabolic effects were due to transactivation[3]. However, recent studies state that some anti-inflammatory effects are caused by transactivation. Non-genomic effects are evident within minutes because they do not require protein synthesis. These effects are mediated by the cytosolic and membrane bound glucocorticoid receptors[2].

Figure 1: Genomic and non-genomic mechanism of glucocorticoids



Abbreviations: cGR = cytosolic Glucocorticoid Receptor; GC = Glucocorticoid; GRE = Glucocorticoid Receptor Responsive element; MAPK = Mitogen Activated Protein Kinase; Mgr = Membrane-bound glucocorticoid receptor; TCR = T-Cell Receptor; TF = Transcription Factor

Classification of glucocorticoids

The systemically used glucocorticoids are classified according to potency, mineralocorticoid effect and the duration of hypothalamic-pituitary-adrenal axis suppression (Table 1). Potency and mineralocorticoid activity is expressed relative to hydrocortisone. This helps in determining comparable doses. The steroid molecule in glucocorticoids is structurally modified so as to increase the potency and to minimize the mineralocorticoid effect[4].

Based on the duration to suppress the hypothalamic-pituitary-adrenal axis, the glucocorticoids are classified as short, intermediate and long acting. The duration of action is not well correlated with the duration of effect possibly because of the intracellular mechanisms. The actual therapeutic effect is longer[5].

Table 1: Classification of glucocorticoids according to potency, mineralocorticoid effect and the duration of hypothalamic-pituitary-adrenal axis suppression

Medication	Anti-inflammatory potency (relative)	Equivalent potency (mg)	Duration of effect (hyothalamic-pituitary-adrenal axis) (h)	Mineralocorticoid potency (relative)
Short acting				
Hydrocortisone	1	20	8-12	1
Intermediate acting				
Prednisone	4	5	18-36	0.8
Prednisolone	4	5	18-36	0.8
Methylprednisolone	5	4	18-36	0.5
Long acting				
Dexamethasone	25	0.75	>36	0

Pattern of glucocorticoid use

The dose, duration and administration of glucocorticoids depends on the diagnosis, clinical indication and goal of treatment. The potency of the drug is expressed in relation to the dosage. The definitions of low dose therapy through to pulse therapy is presented in Table 2[6].

Table 2: Definition of terms for glucocorticoid dosages

Dose	Definition
Low	≤7.5mg prednisone equivalent/ day
Medium	>7.5mg but ≤30mg prednisone equivalent/day
High	>30mg but ≤100mg prednisone equivalent/day
Very high	>100mg prednisone equivalent/ day
Pulse therapy	≥250mg prednisone equivalent/ day for 1 day or a few days

Primary immunosuppressive treatment with glucocorticoids

Glucocorticoids are pivotal in the management of systemic vasculitis, myositis and polymyalgia rheumatica. In polymyalgia rheumatica, monotherapy with glucocorticoid at 15mg prednisone or equivalent daily can achieve remission[7].

Glucocorticoids plays an important role in the management of giant cell arteritis. Empiric high dose pulse therapy of glucocorticoids should be initiated on suspicion of giant cell arteritis with acute visual loss or ischemic stroke. This should be followed by high dose maintenance oral prednisone or equivalent[8].

Pulse therapy

Pulse therapy is the administration of high glucocorticoid doses over a short period of time. In connective tissue disorders, pulse therapy is indicated for treatment of flares or disease induction[9]. 1000mg of methylprednisolone given intravenously for a period of three days is the standard pulse dose.

High and medium doses

High dose glucocorticoids in addition to other immunosuppressive drugs like cyclophosphamide are the cornerstone in the treatment of systemic vasculitis[10]. Intermittent treatment with high dose is also beneficial in acute gout attacks. A five day course of 35mg prednisone improved pain scores in patients with acute gout[11].

Low dose

Low dose glucocorticoid with DMARDs is often utilized in the management of rheumatoid arthritis. Glucocorticoids use has led to improvement in both clinical parameters and acute phase reactions[12,13].

Very low doses of glucocorticoids (<5mg of prednisone or equivalent) can sustain remission in patients with rheumatoid arthritis with minimal adverse effects[14]. A prospective study to validate the risk-benefit ratio of this study is currently ongoing[15].

Numerous studies have reported that the use of low dose glucocorticoids in early rheumatoid arthritis has a disease modifying effect[16,17]. The disease modifying effect or retardation of joint damage persists for four years in spite of using low dose glucocorticoids for a period of two years[18].

Local application of glucocorticoids

Intraarticular injection of glucocorticoids can be considered in patients with persisting non-infective arthritis. The effectiveness of this treatment depends on numerous factors like the joint involved, the severity of arthritis, amount of synovial fluid and the injection technique[19]. Triamcinolone hexacetonide was shown to have the longest effect[20].

Adverse effects

Glucocorticoids can cause frequent and serious adverse events. The adverse effects occur more frequently with prolonged use of high doses of glucocorticoids although some patients get these adverse effects at low doses[21]. However, there is scarcity of high quality data on the occurrence of adverse effects of glucocorticoids as most of the studies on glucocorticoid toxicity are either observational or retrospective[22]. This is further confounded by the fact that the adverse effects caused by glucocorticoids cannot be differentiated from complications of the disease or as other comorbidities. The adverse effects can be avoided or managed appropriately if glucocorticoids are used wisely.

Osteoporosis

Osteoporosis is a debilitating complication of glucocorticoid. The major risk factors are cumulative dose and the duration of glucocorticoid use[23]. Prolonged exposure to doses as low as 2.5mg – 5mg can increase the risk of vertebral fractures. Glucocorticoids almost doubles the risk of vertebral fractures. At least one patient out of four who have been on long term glucocorticoid develop a low energy fracture[24].

Bone loss occurs almost immediately after initiation of glucocorticoids. It mostly affects the vertebral bones because of its high trabecular content[25]. It also changes the architectural integrity of the bone.

Currently, there are effective prevention and treatment options, which can result in reduction of morbidity and mortality associated with glucocorticoids induced osteoporosis[26]. If glucocorticoids are meant to be given for more than three months, a baseline bone mineral density should be measured and then repeated annually. Glucocorticoid induced osteoporosis can be prevented by using the minimal effective glucocorticoid dose, calcium and Vitamin D supplementation in addition to physical activity. Active osteoporosis is usually treated using anti-resorptive drugs like bisphosphonates.

Avascular necrosis of bone (osteonecrosis)

About forty percent of patients on long term high doses of glucocorticoids present with osteonecrosis of the bone[27]. Patients usually present with persistent joint pains and decreased range of motion. Treatment mainly involves joint replacement surgery and bisphosphonates[27].

Myopathy

The most common drug induced myopathy is caused by glucocorticoid. This is characterized by fatigue, painless muscle weakness and muscle atrophy. It can either be acute or chronic. Discontinuation of the glucocorticoid usually results in increased muscle strength within four weeks[28].

Effect on glucose metabolism

Glucocorticoids have a dose dependent effect on glucose metabolism. The development of *de novo* diabetes is uncommon. Patients with a history of glucose intolerance or diabetes have difficulty in controlling their blood sugar levels when started on glucocorticoids.

Glucocorticoid induced hyperglycemia is multifactorial and include increased age, obesity, family history of diabetes, and gestational diabetes. Dysglycemia may improve with dose reduction and usually reverses when the glucocorticoids are discontinued. However some patients may develop persistent hyperglycemia that may require treatment with anti-diabetic agents[29].

Dyslipidemia

Glucocorticoids increases the synthesis of Very Low Density Lipoprotein (VLDL) and accumulation in the liver. All types of abnormal lipid profiles have been reported with use of glucocorticoids and management should be based on general clinical practice[30].

Weight gain and Cushingoid features

Weight gain and Cushingoid features are troubling side effects of glucocorticoids. It has been reported that there is a 4-8% increase in body weight when doses as little as 5mg of prednisone or equivalent are used for two years[31].

Adrenal suppression

Long term use of glucocorticoids leads to adrenal gland suppression due to hypothalamic pituitary axis suppression. Patients on chronic glucocorticoids may have an Addisonian like crisis if the glucocorticoids are discontinued abruptly or tapered off quickly[32]. Clinical AS tends to occur after glucocorticoid exposure for more than two weeks. Higher dose of glucocorticoids is a known risk factor.

In order, to prevent Addison crisis in patients undergoing chronic glucocorticoid therapy, it is recommended that the steroid are tapered or weaned off slowly. Glucocorticoid withdrawal should never be abrupt. Glucocorticoid withdrawal is indicated when their use is no longer indicated or when significant and uncontrollable side effects occur. Several tapering regimens have been published[33].

Patients who take any steroid dose for less than two weeks can abruptly stop treatment. They do not develop HPA axis suppression. The objective of tapering is to initially reduce the therapeutic dose (2.5mg every 3-4 days over a few weeks) to physiological dose (7.5mg / day prednisone or equivalent) and then proceed with further withdrawal to permit recovery of the HPA axis (1mg/d of prednisolone or equivalent every 2-4 weeks). This depends on the patient's general condition, until the medication is discontinued[34]. Other tapering regimens switch patient to alternate dosage of glucocorticoids before discontinuation[35]. Irrespective of tapering regimen used, if GC withdrawal syndrome, adrenal insufficiency or exacerbation of underlying disease occurs, the dose given at that time should be increased or maintained for a longer period of time.

Gastrointestinal side effects

Glucocorticoids increase the risk for gastritis, peptic ulcer disease and gastrointestinal bleeding. This risk rises when combined with a non-steroidal anti-inflammatory drugs[36]. Other gastrointestinal complications include visceral perforation, hepatic steatosis and acute pancreatitis.

Hypertension

The risk of hypertension increases by two fold in patients taking glucocorticoids. The risk is associated with cumulative dosage of glucocorticoids[21]. The risk of hypertension is higher in elderly patients. Hypertension occurs due to an imbalance between vasoconstriction and vasodilation further compounded by weight gain associated with corticosteroid use[37].

Cardiac side effects

There is a 2-4 fold increased risk of cardiovascular disease in patients using 7.5mg or more of prednisolone[38]. This is due to hypertension, dysglycemia and hypertriglyceridemia. Glucocorticoids also predispose to arrhythmias[39]. The cardiac adverse events are dose dependent and the risks decreases on discontinuation of the medicine. Rarely, intravenous pulse therapy with methylprednisolone has caused sudden death[40].

Dermatologic side effects

Chronic glucocorticoid usage causes skin atrophy by preventing secretion of collagen and hyaluronic acid by fibroblast[31]. This dermatoporosis is characterized by skin thinning and formation of telangiectasia and haematoma under the skin. This leads to poor wound healing with

subsequent loss of skin barrier function[41]. Higher doses of glucocorticoids causes steroid acne, hirsutism and hair loss[31].

Neuropsychiatric side effects

A varied number of neuropsychiatric symptoms can occur with glucocorticoids. They range from minor effects such as mood changes, irritability to major effects like depressive disorders, memory loss, psychosis, dementia and delirium[42]. The neuropsychiatric disorders are more common, about 52%, and most disturbing in patients who are taking more than 20mg of prednisone or equivalent for more than three months.

Initially, the patient experiences optimism, this is then replaced by depression. One in six patients will develop depression while on corticosteroids. Patients who take a short course of high dose corticosteroid tend to develop mania and hypomania rather than depression[43]. In majority of patients the symptoms resolve in 6 weeks after discontinuation of treatment. Furthermore, recovery is faster for patients with delirium than those with depression or psychosis[44].

Ophthalmologic side effects

The two common ophthalmologic adverse effects are cataract and glaucoma[45]. This risk increases with cumulative dose and treatment length. Cataracts occur in 11%-15% of patients on chronic glucocorticoid treatment[45]. However, some patients develop posterior sub capsular and cortical cataract even in doses less than 5mg/day[21]. Glucocorticoids increase intraocular pressure in 18%-36% of patients. This is worse in patients with prior glaucoma[31]. Glucocorticoids causes dysfunction of the trabecular meshwork hence unable to drain the aqueous humor[46]. The IOP returns to normal after discontinuation of glucocorticoids in 2-4 weeks. Other ophthalmologic side effects include mydriasis, ptosis, central serous chorioretinopathy, herpetic keratitis and cytomegalovirus retinitis.

Immunologic side effects

Chronic use of corticosteroids subdues cell mediated immunity and alters monocyte functions. This predisposes to intracellular infections[47]. The risk of infection increases with high doses. Corticosteroids makes patients vulnerable to viral, bacterial, fungal and parasitic infections. Furthermore, it can lead to reactivation of latent infections. Diagnosis may be challenging as unusual organisms may be involved and classic manifestations of infection may be masked.

New glucocorticoid formulations

Modified release prednisone

The symptoms of RA, namely joint stiffness, swelling and pain change in a circadian fashion. The symptoms are usually worse in the morning. This is because the levels of inflammatory cytokines are higher in the early hours of the day[48]. Modified Release (MR) prednisone is a new formulation of prednisone, that delays release of prednisone hence allowing adequate concentration of prednisone at night so as to mitigate the effects of increased pro-inflammatory cytokines at night. It significantly reduces interleukin 6 levels and morning symptoms when compared with control treatment. Furthermore, it does not increase the risk for adrenal suppression[49-51].

Liposomal glucocorticoids

Liposomal glucocorticoid is a modified drug delivery system whereby the drug is directly targeted to the synovial capsule[52]. Unlike, intra-articular injection, liposomal glucocorticoids are not rapidly cleared from the synovium into the circulation by virtue of their size and chemical composition[53]. This leads to less side effects as the drug is concentrated at the synovium with reduced exposure to non-target sites.

Selective GC Receptors Modulators (SGRM)

Glucocorticoids bind to glucocorticoid receptors whereby they may either cause transactivation or transrepression. Transrepression is mostly responsible for the anti-inflammatory effect while transactivation is responsible for the adverse effects of glucocorticoids. The SGRMs promote transrepression over transactivation[54], and hence have lesser metabolic adverse effects than the conventional glucocorticoids.

Recommendations for clinical practice

To ensure safe use of glucocorticoids in rheumatic diseases, several recommendations have been published. The main aim of these recommendations is to achieve optimal therapeutic glucocorticoid effect with minimal adverse effects as there is no absolute safe dose of glucocorticoid null of adverse effects. Certain measures can be undertaken so as to avoid or minimize the adverse effects of glucocorticoids.

Education

Patients should be informed about both the positive and negative effects of glucocorticoids over time. This alleviates unfounded fears, allows early recognition of true adverse effects and improves patients' compliance.

Preventive measures

All patients who are on medium to high dose glucocorticoids are at risk of osteoporosis. Calcium, and Vitamin D should be started with glucocorticoids, while those patients who are at high risk of osteoporosis, should also take bisphosphonates. Several studies have proved that calcium, vitamin D and bisphosphonates can both prevent and treat glucocorticoid induced osteoporosis[55,56].

Use in pregnancy

The fetus is protected from maternal glucocorticoids as glucocorticoid cannot traverse the placenta. Furthermore, cortisol and prednisolone are converted to inactive metabolites by the placental enzyme 11β hydroxysteroid dehydrogenase. However, some fetuses have intrauterine growth restriction, low birth weight or oral cleft when given antenatal steroids. It is advisable to avoid high dose steroids in the first trimester[57].

Conclusion

Glucocorticoids are very effective in the management of rheumatologic diseases. However, their use is curbed by the occurrence of adverse effects. There is no absolutely safe dose of glucocorticoids, only relatively safer doses. These adverse effects can be abated if glucocorticoids are used prudently. Clinical use of newer glucocorticoid drugs with no adverse effects will not occur in the near future.

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Research article

The severity of rheumatoid arthritis at the first rheumatology consultation and factors associated with initial structural damage in sub Saharan patients

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Abstract

Background: The severity of Rheumatoid Arthritis (RA) at diagnosis has not been fully described in sub-Saharan Africa in recent years, nor have been the factors associated with it.

Objective: The aim of this study was to determine the frequency of severe RA at the first rheumatology consultation and assess the factors associated with this early severity.

Design: This was a retrospective study.

Methods: The study was carried out in the rheumatology service of the Yaoundé Central Hospital, Cameroon. Files (one patient = one file) of patients diagnosed with RA during January 2004-May 2018 were included. RA severity was defined by the presence of at least one of these markers: Disease Activity Score-28 with Erythrocyte Sedimentation Rate (DAS28-ESR) > 5.1, initial structural damage on hand X-rays which was defined by a Larsen score ≥ 2 per joint and the presence of Rheumatoid Factor (RF) and/or Anticitrullinated Protein Antibodies (ACPA). Files with no information to assess disease severity at the time of diagnosis were excluded. Data were analyzed with Epi-info version 7.0. Statistical significance was set at p-values less than 0.05.

Results: Forty-nine patients were included. Their mean age was 48 ± 14 years. Eighty percent of them were females. Sixty-seven percent had established RA, 33% had early-stage RA and two patients had ever smoked. None of them had received biological disease-modifying antirheumatic drugs. RA was severe in 82% of patients, with DAS28-ESR > 5.1 in 71%, positivity of at least one autoantibody found in 63% to 82%, and initial structural damage found in 55% of them. Initial structural damage was only associated with the presence of ≥ 10 swollen joint counts.

Conclusions: RA was severe from the onset in most patients and structural damage was associated with the presence of ≥ 10 swollen joint counts.

Key words: Rheumatoid arthritis, Severity, Initial presentation, Structural damage, Sub-Saharan Africa

Introduction

Rheumatoid Arthritis (RA) is a chronic inflammatory autoimmune systemic disease. It affects 0.5-1% of the general population and progressively leads to irreversible joint destruction that causes disability[1]. Indeed, RA was responsible for 3.4 million disability-adjusted life years during 1990-2017[2]. Furthermore, patients with long-standing and severe RA have a shorter life expectancy of up to 10 years compared to normal subjects[3]. These high morbidity and mortality are strongly related to the severity of RA since the most severe forms are the most likely to cause (early) joint destruction[4] and are often associated with a high prevalence of comorbidities[5]. A systematic literature review including 18 studies published over a 44-year period defined severe RA from the onset as RA presenting with structural damage, autoantibody positivity, biological inflammation or high swollen joint counts[4].

In sub-Saharan Africa, RA was largely unknown until the beginning of the 21st century, resulting in long diagnostic delays in the first studies[6]. Previous hospital based studies conducted in

South, West and Central Africa have shown that RA is severe in most patients[7-13]. Given the improving awareness for RA in sub-Saharan Africa together with the ongoing reduction of severe cases of RA from the onset as recently demonstrated by the Norfolk Arthritis Register study[14], we conducted this contemporary study to determine the frequency of severe RA from the onset and assess the factors associated with initial structural damage.

Materials and methods

We carried out a cross-sectional retrospective study using files of patients (one file = one patient) aged ≥ 18 years and diagnosed with RA from January 2004 to May 2018 in the Rheumatology service of the Yaoundé Central Hospital. The diagnosis of RA was based either on the 1987 American College of Rheumatology criteria[15] or the 2010 ACR/European League Against Rheumatisms (EULAR) criteria[16] or both. Files with no information to assess severity at the time of diagnosis were excluded.

RA was considered severe from the onset if at least one of the following characteristics was found at diagnosis[4,17]; (i) disease activity score 28 with erythrocyte sedimentation rate (DAS28-ESR) > 5.1, (ii) initial structural damage on hand X-rays which was defined by a Larsen score ≥ 2 per joint[18] (iii) and the presence of Rheumatoid Factor (RF) and/or Anticitrullinated Protein Antibody (ACPA).

Bivariate analyzes were conducted to assess the factors associated with initial structural damage. Candidate factors included in the model were: number of tender joints ≥ 10, number of swollen joints ≥ 10, CRP ≥ 6 mg/l, ESR ≥ 20 mm, DAS28-ESR > 5.1, positive RF, positive ACPA and the presence of extra-articular features. The significance threshold was set at $\alpha = 0.05$. Data were entered in Microsoft excel 2013 and analyzed with Epi info version 7.0 software. Ethical clearance was granted from the Institutional Ethical Review Board of the Faculty of Medicine and Biomedical Sciences of the University of Yaoundé I and administrative authorizations before data collection.

Results

Baseline characteristics of the study population: Of the 102 files retrieved, 49 were included in this analysis. Most of them were females with established RA, and two had ever smoked. Twenty-two percent of patients had extra-articular features, and 55% had radiographic erosions on extremity joints. The mean DAS28 was 5.7 ± 1.1. Eighty percent and 88% of patients respectively received methotrexate and glucocorticoids as initial treatments. None of these patients had received biological disease-modifying antirheumatic drugs. These characteristics are detailed in Table 1.

Table 1: Characteristics of the study population

Age (mean ± SD), years	48 ± 14
Females, n (%)	39 (80)
Ever smoked, n (%)	2 (4)
Diagnostic delay, median (interquartile range 25 to 75); years	36 (12-84)
Established RA*, n (%)	33 (67)
Morning stiffness > 30 minutes, n (%)	12 (24)
Hand deformations	11 (22)
Ulnar deviation, n (%)	6 (12)
Boutonniere deformity, n (%)	6 (12)
Z-deformity, n (%)	3(6)
Camel back deformity, n (%)	2 (4)
Swan neck deformity, n (%)	1 (2)
DAS28-ESR	5.7 ± 1.1
NSAIDs, n (%)	37 (75)
Glucocorticoids, n (%)	43 (88)
Methotrexate, n (%)	39 (80)
Hydroxychloroquine, n (%)	9 (18)
Sulfasalazine, n (%)	2 (4)

Established RA* established rheumatoid arthritis: duration ≥ 2 years; DAS28-ESR = disease activity score-28 with erythrocyte sedimentation rate; NSAIDs = non-steroidal anti-inflammatory drugs

Frequency of the severity of RA: According to the predefined criteria, RA was severe in 40 (82%) patients. Thirty-five (71%) had high disease activity, 40 (82%) had positive RF, 31 (63%) had positive ACPA and 27 (55%) had initial structural damage. The frequency of markers of severity is depicted in Table 2.

Table 2: Frequency of markers of RA severity

Clinical	No. (%)
Increased number of tender joints (> 10), n (%)	27 (55)
Increased number of swollen joints (> 10), n (%)	11 (22)
Extra-articular features, n (%)	11 (22)
Fever, n (%)	9 (18)
Weight loss, n (%)	9 (18)
Anaemia, n (%)	5 (10)
Sicca syndrome, n (%)	3 (6)
Subcutaneous nodules, n (%)	2 (4)
Pulmonary fibrosis, n (%)	1 (2)
Pericarditis, n (%)	1 (2)
Fatigue, n (%)	1 (2)
Biological	
Increased ESR (>20 mm), n (%)	43 (88)
Increased CRP (> 6 mg/l), n (%)	41 (84)
RF positivity, n (%)	40 (82)
ACPA positivity, n (%)	31 (63)
Radiographic	
Larsen score per joint ≥ 2	27 (55)
Disease activity	
DAS28-ESR> 5.1	35 (71)

Factors associated with initial structural damage: Initial structural damage was associated to the presence of more than 10 swollen joints: odds ratio 18 (95% confidence interval: 1.05-506.06), p-value = 0.04.

Table 3: Bivariate analysis of factors associated with initial structural damage

Variables	OR (95% CI)	P-value
Number of tender joints > 10	4.67 (0.41-130.66)	0.23
Number of swollen joints > 10	18 (1.05-506.06)	0.04
Extra-articular features	3.67 (0.26-45.16)	0.3
CRP ≥ 6 mg/l	0.33 (0.01-16.14)	0.49
ESR ≥ 20 mm	-	0.51
Positive RF	-	0.07
Positive ACPA	0.94 (0.1-10.34)	0.68
DAS28-ESR > 5.1	0.67 (0.07-7.68)	0.56

Discussion

In this study, we found that 82% of patients had severe RA at the onset; i.e. 71% with high disease activity, 63 to 82% with positivity of at least one autoantibody, and 55% with initial structural damage. Initial structural damage was associated with only the presence of ≥ 10 swollen joint counts.

The results of this study are in concert with data from Mathieu and colleagues' systematic review[4], which found a high prevalence of markers of RA severity in 18 studies published from 1998 to 2009 and including European and American patients. These results are also consistent with previous studies that found a high frequency of markers of severity at the time of diagnosis of RA in African patients with some differences in proportion[9-13], probably as a simple reflect of differences in sample sizes and methods for calculation of the DAS28. Furthermore, the prevalence of autoantibodies is even more difficult to compare between studies in sub-Saharan Africa because detection methods vary from one study to another[9-13]. The prevalence of structural damage found in this study is however comparable to those described in Senegal[13] and Democratic Republic of the Congo[10], although those studies assessed structural damage using the score of van der Heijde unlike here where the score of Larsen was rather used.

This high frequency of markers of early RA severity is likely to be underpinned by genetic and environmental factors[19]. Among the genetic factors, the shared epitope of HLA-DRB1 is the one that has already been identified in sub-Saharan African patients[9,10]. In fact, it has been associated with a high production of autoantibodies in both sub-Saharan Africans and Caucasians[9]. The high production of autoantibodies would promote a high level of inflammation, severe disease activity, and therefore significant structural damage. Inflammation would promote structural damage during RA through the action of pro-inflammatory cytokines such as tumour necrosis factor alpha which activates osteoclasts, thus promoting osteolysis[20]. However, the shared epitope is probably not the main determinant of this severity, since it is absent in the majority of sub-Saharan African patients, despite prevalence rates of autoantibodies comparable to those in Caucasians[9,10]. The effect of other non-HLA genes such as PTPN22[19] should therefore be explored locally. Among environmental factors, tobacco does not appear to contribute significantly to the (early) severity of RA in sub-Saharan Africa. Indeed, smoking is only documented in a minority of patients in most series as in this study[9,10,12]. Since most sub-Saharan African women have lifetime exposure to wood smoke, household air pollution is an environmental factor that should be specifically investigated with respect to RA in sub-Saharan Africa[21]. The long diagnostic delay due to a low index of suspicion and late referral to rheumatology would also contribute to this high frequency of early RA severity[9,13]. Of note, there has been a gradual decrease in RA activity over time in the United Kingdom as a result of increasing early referral of patients to rheumatologists[14].

These results are relevant in several ways for national and regional rheumatologists as well as local stakeholders. In particular, strategies aimed at early detection and management of RA should be part of chronic non-communicable disease programs already existing in most sub-Saharan African countries. These strategies could involve the local implementation of World arthritis day (12th October), during which sensitization campaigns targeting the general public and non-rheumatologists health professionals could be organized. Extension of rheumatology training programs across countries and strengthening of RA lectures in medical students' curricula could further help to improve RA diagnosis within the region. Diagnosed and treated patients need to be followed up more closely. A support from international arthritis funding bodies is also warranted to improve the availability and affordability of effective biological Disease-Modifying Antirheumatic Drugs (bDMARDs), as this study suggests that a high proportion patients need to be started on bDMARDs within three months of diagnosis[4].

The small sample size of this study precludes strong conclusions. Information bias related to the retrospective nature of the study did not allow us to specify all the pertinent markers of RA severity (e.g. health assessment questionnaire), or to stratify RA severity with respect to disease duration. We hope this study will foster future relevant high-quality research accounting for the above mentioned shortcomings.

Conclusions

Most patients presented with early severe RA, and structural damage was associated with a high number of swollen joint counts. These findings should be confirmed in future local large prospective studies.

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Ethics approval and consent to participate

The Institutional Ethical Review Board of the Faculty of Medicine and Biomedical Sciences of the University of Yaoundé I approved the study. Informed consent was not requested as this was a retrospective study. We have respected the terms of the Helsinki Declaration.

Consent for publication

All authors consented to publish the manuscript in African Journal of Rheumatology.

Competing interests

We declare that we have no competing interests.

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Research article

Assessment of disease activity and health-related quality of life in patients with systemic lupus erythematosus at Kenyatta National Hospital

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Abstract

Objective: To determine disease activity in Systemic Lupus Erythematosus (SLE) patients and correlate it with quality of life.
Design: Cross-sectional descriptive study.
Methods: SLE patients fulfilling SLICC 2012 criteria for SLE were included in this cross-sectional study. Disease activity was measured using the clinical Systematic Lupus Erythematosus Disease Activity Index (SLEDAI-2K). Quality of life was assessed using the self-administered LupusQoL.
Results: The study group had 62 patients (60 females and 2 males) with a mean age of 34±11.8 years, and the mean duration of follow up was 36 months. The mean cSLEDAI-2K score was 7±5.2, and the median disease activity score was 7. All the domains of LupusQoL were impaired. Higher disease activity scores were associated with lower QoL scores in the domains of physical health, pain, burden to others, body image and general health. Patients with renal disease had significantly lower QoL compared to other patients, and the pain, intimate relationships and body image were most affected. Age and disease duration had a positive correlation with QoL. Disease duration (p=0.01), was associated with a better QoL in the pain, emotional health and body image domains.
Conclusion: This study is showing a low HRQoL in those with active disease mainly in the young age group. A recent diagnosis of lupus and the presence of renal disease was associated with a more reduced quality of life.

Key words: SLE, Disease activity, Health-Related Quality of Life, cSLEDAI-2K, LUPUSQoL

Introduction

Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disorder characterised by inflammation in different organ systems. It has a highly variable clinical presentation that ranges from mild cutaneous involvement to life-threatening multi-organ failure. It has an unpredictable chronic course, with alternating periods of quiescence and exacerbations of disease activity. SLE predominantly affects young women causing significant morbidity and mortality[1].

Disease activity measures the potentially reversible manifestations of the inflammatory process. However, assessment of physical health is insufficient to account for the impact of the disease. Quality of life serves as the patients' subjective perception of living with the disease. Health-Related Quality of Life (HRQoL) is a multidimensional concept that provides the patients' self-evaluation of how the disease affects their physical, social, and psychological wellbeing[2].

SLE disease activity and damage scores are poor surrogates of HRQoL because results linking these measures and QoL are non-uniform[3,4]. High disease activity negatively affects the patients' quality of life[5]. In Kenya, a low QoL in SLE patients' has been described[6]. Besides, multiple studies have been done assessing individual organ systems[7,8]. The purpose of this study was to assess the impact of disease activity on HRQoL in SLE patients attending the rheumatology clinic at the Kenyatta National Hospital. It would also serve as an audit of the adequacy of care provided at the clinic while providing the patients perspective regarding their treatment.

Materials and methods

Patient selection: This was a cross-sectional descriptive study conducted at Kenyatta National Hospital rheumatology and renal outpatient clinics. The institutional ethics review committee approved the study. Informed

consent was obtained before enrolment. Ninety patients were reviewed, and 62 patients who fulfilled the Systemic Lupus International Collaborating Clinics 2012 classification criteria for SLE were consecutively recruited. One patient refused to consent, and 28 with overlap syndromes were excluded.

Data collection: Data collected included demographic characteristics (age, gender, marital status, education level, employment status) and disease duration. Disease activity was evaluated using the clinical Systemic Lupus Erythematosus Disease Activity Index 2000 (cSLEDAI). The disease-specific LupusQoL assessed the health-related quality of life. The treatment characteristics: type of drugs used (use of glucocorticoids, use of immunomodulators and immunosuppressants, e.g., hydroxychloroquine, azathioprine, biologics) and daily dosage were corroborated with the patients' medical records.

Instruments: Disease activity was evaluated by clinical SLEDAI, which omits complement and ds DNA. SLEDAI-2K is a valid, widely used index with excellent cross-cultural compatibility[9]. The cSLEDAI has been validated against the SLEDAI-2K and shown a high correlation (r=0.924)[10]. The omission of the immunological variables makes it cheaper to administer in a resource-constrained setting like Kenya.

Disease activity was scored by 22 clinical and laboratory parameters instead of the original 24 variables. The descriptors were scored if they were present at the time of the interview or in the preceding 30 days. cSLEDAI is an ordinal scale that gives a composite score ranging from 0-105. Patients scoring 0-5 were classified as having mild disease, those scoring between 6-12 were categorised as moderate, and those with scores higher than 12 were defined as having severe disease.

The health status was assessed using the disease-specific LupusQoL©, which was self-administered[11]. LupusQoL contains 34 items in 8 domains. Each item was scored with a Likert type scale to grade the patients' response with 1 (all the time), 2 (most of the time), 3 (a good bit of the time), 4 (occasionally), and 5 (never). The eight domains are physical health (8 items), pain (3 items), planning (3 items), intimate relationships (2 items), the burden to others (3 items), emotional health (6 items), body image (5 items) and fatigue (4 items). The response from the items was calculated per domain, and the mean domain score was then obtained by dividing the total score by the number of items in that domain. The mean raw domain was divided by 4 then multiplied by 100 to obtain the transformed domain score. Scores range from 0 (worst) to 100 (best). Higher scores indicate better quality of life.

Data analysis: Descriptive statistics were used to summarise the data on socio-demographic and patient characteristics. Categorical data were summarised as numbers and percentages, while continuous data were summarised as mean and standard deviation/medians and interquartile ranges, as appropriate. Pearson correlation coefficients were done to compare LupusQoL scores with disease activity, age, and disease duration. A p-value of ≤0.05 was considered to be significant. All analyses were performed on the Statistical Package for Social Sciences (SPSS) software version 23 (SPSS©, Chicago, IL, USA).

Results

The 62 patients included in the study were 60 females and 2 males. There were 56 patients from the rheumatology clinic and six from the renal clinic. The mean age was 34±11.7 years, range 17-61 years. Amongst all respondents, 36 (58.1%) were married, 27 (43.6%) had attained a tertiary level of education, and 32 (51.6%) were employed. The median disease duration was 36 (50%) months, range 1-324 months. The socio-demographic characteristics are as shown in Table 1.

Table 1: Socio-demographic characteristics of the patient population

Variable mean±SD or n (%)	SLE patients (n=62)
Age (years), mean (SD)	34±11.8
Gender, female, *n* (%)	60(96.8)
Marital status	
Married	36 (58.1)
Single	26 (41.9)
Level of education, n (%)	
Primary (0-8 years)	15(24.2)
Secondary (9-12 years)	20(32.2)
Tertiary (>12 years)	27(43.6)
Employment status	
Employed	32(51.6)
Unemployed	30(48.4)
Disease duration, n (years)	
<1 year	20(32.3)
1-5 years	24(38.7)
≥5 years	18(29.0)
Treatment characteristics	
Use of glucocorticoids	49(79.0)
Use of HCQ	48(77.4)
Use of AZA	20(32.2)
Use of Mycophenolate	17(27.4)
Other immunosuppressants	6(0.09)

The other immunosuppressants drugs used were cyclophosphamide, cyclosporin, leflunomide, and methotrexate. HCQ; hydroxychloroquine, AZA; azathioprine

Nine (14.5%) of the respondents were not on any medication at the time of the interview. Only two patients were on hydroxychloroquine monotherapy. HCQ and steroids were prescribed to 77.4% of patients in conjunction with other immunosuppressants. The median dose of steroids used was 11.2 mg (range 2.5-60mg). There was no patient on biologic disease-modifying drugs.

The mean disease activity score was 7 (SD ± 5.2), and the median disease activity was 7 (range 0-18). Half of the patients in the study had moderate to severe disease activity. There were eight patients in remission on therapy (Table 2).

Table 2: Disease activity score

SLEDAI-2K	Frequency n=62 (%)
Disease Activity Score	
Mild	31 (50.0)
Moderate	15 (24.2)
Severe	16 (25.8)
Low disease activity	8 (12.9)

(Max disease activity score=105, remission=0, low disease activity score ≤3 [HCQ], ≤4 [steroids])

No patients presented with seizures, psychosis, cranial nerve disorders, lupus headache, or cerebrovascular accident at the time of assessment. There were 13 patients with visual abnormalities [optic atrophy-2], [glaucoma-2], [age-related macular degeneration-3] and [hydroxychloroquine toxicity-6]. None of the retinal changes were indicative of active disease. Among the 62 respondents, 33 (53.2%) had renal involvement with 31(50%) having proteinuria. The other clinical characteristics are shown in Table 3.

Table 3: Clinical and laboratory characteristics of SLEDAI-2K

Descriptor	Score	Frequency n=62 (%)
Proteinuria	4	31 (50.0)
Haematuria	4	19 (30.6)
Leukopenia	1	17(27.4)
Myositis	4	15 (24.2)
Alopecia	2	9 (14.5)
Pleurisy	2	9 (14.5)
Arthritis	4	7 (11.3)
Thrombocytopenia	1	7 (11.3)
Rash	2	5 (8.1)
Pyuria	4	4 (6.5)
Vasculitis	8	3 (4.8)
Mucosal ulcers	2	3 (4.8)
Fever	1	2 (3.2)
Rash	4	1
Psychosis	8	1
Urinary casts	4	1
Organic brain disorder	8	1

The SLEDAI score was calculated based on the clinical and laboratory manifestations present at the time of the visit or in the preceding 30 days.

The mean LupusQoL score was 56%±24.4. All the domains of LupusQoL were impaired, especially the domains of intimate relationships, the burden to others, and body image (Table 4). The mean QoL scores amongst the three groups of disease activity were lowest in patients with severe disease activity and highest in patients with mild disease activity (Table 5). The patients with renal abnormalities had significantly lower QoL compared to other patients (r=-0.36, p=0.037) and the pain (p=0.009), intimate relationships (p=0.04), and body image (p=0.01) were most affected.

Table 4: Average quality of life (Mean LupusQoL)

LupusQoL domains mean±SD (range)	SLE patients (n=62)	
	Mean (SD)	Range
Physical health	58.2 (28.2)	6.3 – 100
Pain	60.2 (29.8)	8.3 – 100
Planning	65.9 (29.0)	0 – 100
Intimate relationship	50 (38.2)	0 – 100
Burden to others	50.9 (34.7)	0 – 100
Emotional health	62.3 (26.2)	4.2 – 100
Body image	51.0 (30.1)	0 – 100
Fatigue	65.4 (28.7)	6.3 – 100
The average quality of life score	56.0 (24.4)	7.6-99.6

Table 5: The mean LupusQoL scores amongst different groups of disease activity

LupusQoL domain	Disease activity		
	Mild (0-5)	Moderate (6 – 12)	Severe (>12)
	Mean (SD)	Mean (SD)	Mean (SD)
Physical health	63.3 (28.1)	55.2 (31.8)	51.4 (24.4)
Pain	64.5 (30.4)	62.2 (27.1)	50.0 (30.6)
Planning	69.1 (30.0)	63.3 (29.3)	62.0 (27.9)
Intimate relationship	55.2 (38.7)	49.2 (39.7)	40.6 (36.4)
Burden to others	60.9 (34.3)	47.8 (36.3)	34.4 (28.4)
Emotional health	63.0 (30.9)	59.2 (23.0)	63.8 (19.5)
Body image	59.8 (30.9)	45 (26.8)	39.7 (27.8)
Fatigue	66.3 (28.4)	61.3 (29.8)	67.2 (29.6)

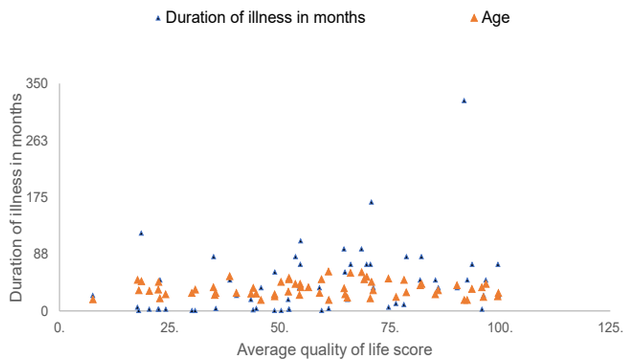
Pearson correlation coefficients were done to correlate the LUPUSQoL scores with disease activity scores, age, and disease duration. Disease activity scores showed a significant negative correlation with the average QoL with the physical health, pain, burden to others, and body image being the worst affected domains. However, the planning, intimate relationships, emotional health, and fatigue domains did not show any correlation with disease activity scores (Table 6).

Table 6: Pearson correlation between the individual quality of life domains and SLEDAI score

LupusQoL domains	SLE patients (n=62)	
SLEDAI (r)		P-value
Physical health	-0.26	0.043*
Pain	-0.28	0.027*
Planning	-0.15	0.255
Intimate relationship	-0.22	0.092
Burden to others	-0.36	0.004*
Emotional health	-0.079	0.540
Body image	-0.34	0.007*
Fatigue	-0.08	0.532
The average quality of life	-0.28	0.026

r=Pearson's correlation coefficient, *p-value ≤0.05
Age and disease duration correlated positively with mean QoL scores (Figure 1).

Figure 1: Correlation between quality of life, age and disease duration



The average quality of life score correlated positively with duration of illness (r=0.31, p=0.01)

Pain, emotional health, and body image domains improved with longer disease duration (Table 7). However, age did not show any significant statistical correlation with any of the LupusQoL domains.

Table 7: Pearson correlation (r) between disease duration and mean LupusQoL score

LupusQoL domains	Pearson Co-efficient r	P-value
Physical health	0.24	0.06
Pain	0.32	0.01*
Planning	0.22	0.07
Intimate relationship	0.25	0.05*
Burden to others	0.13	0.31
Emotional health	0.28	0.02*
Body image	0.34	0.007*
Fatigue	0.23	0.08

*P-value ≤0.05

Discussion

This study is the first prospective study in SLE patients at KNH, exclusively focusing on disease activity. Previously, multiple studies have been done evaluating specific aspects of disease activity. This study sought to evaluate the impact disease activity has on health-related quality of life in patients with SLE.

More than half of the patients had active disease as the median disease activity score was 7. The high disease activity can be attributed to a cumulative effect of multiple barriers, including delays in diagnosis, lack of access to specialists, and the prohibitive cost of treatment, and regular follow up. Diagnostic delays are affected by the heterogeneous nature of the disease, the lack of immunological assays in most laboratories, the long lag period before referral to a specialist, which all add up to cause organ damage and severe disease. However, this score is lower than what has been reported in other African countries[12,13]. Our study omitted ds DNA and complement levels; thus, the total SLEDAI score was lower. These countries also have different population diversity and socio-cultural practices. Persons having African ancestry are prone to having a more aggressive disease course. Similarly, the Hopkins Lupus Cohort, which was a longitudinal study of patients with SLE for more than 28 years, African Americans (38.9%) tended to have a higher disease activity score and a more aggressive chronic course. This pattern has been seen in the Lupus in the minorities: nature versus nurture (LUMINA) cohort that also had multiple ethnicities (n=554)[14-16].

Kidney disease had a significant contribution to the high disease activity. The prevalence of renal dysfunction was 53%. Most of the patients with renal disease were asymptomatic. This delay in diagnosis could be attributed

to a lack of finances to pay for laboratory investigations and fragmentation of care and follow up of patients. Most of the patients were on follow up at the rheumatology clinic while others[6] attend the renal clinic. These two clinics are not integrated, and there are no local protocols to be followed. Thus, patients are managed with varying therapeutic options depending on whether they visit the rheumatologist or the nephrologist.

SLE strongly influences the health status of patients. This study demonstrated a poor global quality of life, with the average QoL mean score being 56%. The results of this study confirm the discriminant validity of LupusQoL in defining outcomes in lupus. As a disease-specific measure, it was able to distinguish between patients with varying degrees of disease severity reliably. These results are similar to other studies that have shown that the overall quality of life in SLE is reduced, albeit with different domains affected[17]. Some studies have reported that ethnicity impacts HRQoL with African Americans having more significant impairment compared to Caucasians[18]. This impairment is further worsened by the greater vulnerability of Blacks to severe disease.

In 2013, the first study done on the quality of life in SLE patients in KNH demonstrated an overall low HRQoL, mean LupusQoL score of 55%[6]. Although the current study demonstrated a marginal improvement in most domains (except for burden to others which worsened), the overall quality of life remains unvaried. The poor quality of life in patients with lupus at KNH contrasts sharply with a better quality of life in patients with rheumatoid arthritis in the same institution. Despite the patients with rheumatoid arthritis having poor disease control, they have a better HRQoL[19]. We can only postulate as to the reason why this is so could be due to the older age of patients with rheumatoid arthritis and better social support. The current study delineated a positive correlation between disease duration and the pain, emotional health, and body image domains. Quality of life has been shown to improve with age. Over time, patients find it easier to accept their disease and the impact it has. Thus they can develop coping strategies. However, other studies have shown contradictory results regarding the effect of age and disease duration[5,20].

Progressive decline in QoL was noted with worsening disease activity. These findings conform to what has been reported elsewhere. Among Egyptian patients, the overall QoL was weak, and an inverse relationship existed between disease activity and QoL. Their scores in the LupusQoL domains were comparable to the ones obtained in our study except for intimate relationships and body image, where they scored significantly higher. Similarly, in India, a negative correlation existed between high disease activity and the physical and psychological aspects of lupus, while the social and environmental aspects were not affected[21]. In South Africa, high disease activity negatively impacted functional ability and health-related quality of life[22]. However, the relationship between disease activity and HRQoL in SLE is not uniform. A lack of correlation between disease activity and HRQoL is present in other settings[23]. The lack of correlation can be attributed to different patient characteristics, different instruments of assessment, the diverse nature of the disease, and the periodicity of symptoms. Patients with renal disease also scored lower in the average QoL compared to patients with the non-renal disease. This pattern was also observed in Egyptian patients and a systematic review[13,24].

Regarding the medications used by patients, there was significant heterogeneity noted in the prescriptions given to patients. The varied prescription patterns are due to multiple factors. Doctors of different cadres evaluate the patients during their clinic visits. The patients attend the rheumatology clinic, and some overlap with the renal clinic. These clinics happen on different days. There is no integrated lupus/renal clinic. These clinics are staffed by specialists consultants and residents from Internal Medicine at different levels of training. There are no local institutional guidelines or any international guidelines adopted for use in our set-up. Although hydroxychloroquine is one of the cornerstone drugs in the management of lupus, only 77% of patients had it prescribed. This percentage remains unchanged compared to another study done in KNH in 2016[7]. This discrepancy was attributed to in part by the cost of the medication, which reported to be expensive by the patients, drug allergies, and other unclear reasons. The median dose of steroids was 11.2mg (range 2.5mg – 60mg), which is higher than the dose needed to achieve remission for patients without renal abnormalities, cardio-pulmonary involvement, or fever[25,26].

The cross-sectional nature of the study was a limitation. It did not account for the periodic nature of the disease. SLEDAI-2K is also inherently limited by the dichotomous nature of the scoring system, which disregards the severity of the abnormalities, thus creating a ceiling effect. The score assigns the same numerical weight, which makes it insensitive to any partial improvement or worsening of active manifestations.

In conclusion, high disease activity portends a worse QoL. Young age, renal disease, and a shorter disease duration adversely affect the HRQoL. It is thus necessary to incorporate measures that provide patient-reported outcomes in routine clinical practice to evaluate better the impact of the disease on the overall health status.

Conflict of interest: None to declare.

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Research article

Rheumatoid arthritis in Ghana - A description of an inception cohort

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Abstract

Objectives: This study outlines disease characteristics in Ghanaian Rheumatoid Arthritis (RA) patients.
Design: A retrospective study.
Methods: The study was conducted by examining the records of 179 RA patients at the Korle-Bu Teaching Hospital Rheumatology Clinic between January 2013 and January 2015. Patient demographic, clinical and laboratory variables were obtained by chart review in a standard data collection form. Analysis was done using SPSS version 23. For all analysis, p values less than 0.05 were considered statistically significant.
Results: The male:female ratio was 1:4.59 with mean age of onset of 41.4 years and disease duration of 64 (12.8-140) weeks. Rheumatoid factor was positive in 78 (43.6%) and anti-cyclic citrullinated peptide in 100 (55.9%). Constitutional symptoms of fever and fatigue were common and anaemia was the most common extra articular feature.
Conclusion: In this first study of RA in Ghanaians, the key findings were similarities between our patients and other West African populations that mimic Caucasian populations in age, sex and joint distribution, a relatively low joint count, few extra articular manifestations and little nodal disease.

Key words: Rheumatoid arthritis, Sub-Saharan Africa, Geographic differences, Disease characteristics

Introduction

Rheumatoid Arthritis (RA) is a systemic autoimmune disease resulting in symmetrical chronic erosive inflammatory polyarthritis that results in joint destruction, disability and increase mortality as well as placing a significant burden on health care systems.

With an estimated global prevalence of 1%, RA is one of the most common chronic diseases[1,2]. RA is believed to have first been reported in Europe in the 17th century and subsequently described in the Americas among Native American Indians[3]. It was not until the middle of the 20th century that the first case of RA in Africa was described[4].

Despite being a leading cause of chronic morbidity in the developed world, little is known about the disease burden in Africa despite its potentially life threatening systemic manifestations and profound morbidity[2,5].

Majority of studies in Africa were concentrated in a few countries notably; South Africa, Nigeria and Uganda, with the majority of the continent having no available data. As a result the extent of the burden of RA in Africa is largely unknown[5]. Furthermore, most of the data for Africa has come from studies conducted between the 1950s and 1980s[6].

Variation in prevalence and incidence rates across different racial backgrounds has been noted, with differences in susceptibility, age, disease course, clinical expression, clinical and laboratory findings and this has been attributed to the possible influence of genetic and environmental factors.

We sought to examine a cohort of RA patients in Ghana to determine disease characteristics compared to other populations and this is the account of our findings.

Materials and methods

A retrospective study was conducted examining the records of the period of January 2013 to January 2015. We included patients diagnosed with rheumatoid arthritis according to the ACR criteria[7] at the Rheumatology Unit of the Korle-Bu Teaching Hospital. All patients met at least four of the ACR classification criteria for RA. Patients without complete medical details or follow up or those who did not meet RA ACR diagnosis criteria were excluded. The Ethics Committee of the Korle-Bu Teaching Hospital approved the study.

Information on patient demographic, clinical and laboratory variables over the course of disease was obtained by chart review, and collected in a standard data collection form created for that purpose. The clinical or laboratory variables were

registered as "present" or "absent" for each specific patient at the moment of diagnosis and then at any time during the course of the disease.

Statistical analysis: Descriptive statistical data was computed. Data analysis was done using SPSS version 23. Continuous variables were presented as means ± SD or Median (IQR). Categorical or nominal variables were expressed as proportions and compared using Chi-squared test or Fishers exact test as appropriate.

Results

One hundred and seventy nine patients with rheumatoid arthritis seen between the years 2013 to 2015 were evaluated. Females constituted majority 147 (82.1%) of patients and were mostly professionals and in the sales and trader sector of employment. Few people smoked in the cohort and alcohol use was low (Table 1).

Table 1: Socio demographic and clinical characteristics of rheumatoid arthritis patients

Socio-demographic variables	Frequency (n)	(%)
Sex (n=179)		
Male	32	17.9
Female	147	82.1
Occupation (n= 157)		
Administrative indoor	113	72.0
Outdoor	44	28.0
Smoking history (n=179)		
No	176	98.3
Yes	3	1.7
Alcohol use (n=179)		
No	153	85.5
Yes, but not significant use	26	14.5
Clinical characteristics	Frequency(n)	(%)
Medical history (n=179)		
None	143	79.9
Hypertension	23	12.8
Diabetes	2	1.1
Other	11	6.1
Parity (n =179)		
Para 0	154	86.0
Para 1 or more	25	13.9
Morning stiffness (n=179)		
No	99	55.3
Yes	80	44.7
Nodules (n=179)		
No	172	96.1
Yes	7	3.9
Oral ulcers (n=179)		
No	164	91.6
Yes	15	8.4
Fatigue (n=179)		
No	154	86
Yes	25	14
Malaise (n=179)		
No	169	94.4
Yes	10	5.6
Fever (n=179)		
No	138	77.1
Yes	41	22.9
Eye changes (n=179)		
No	174	97.2
Yes	5	2.8
Skin rash (n= 179)		
No	157	87.7
Yes	22	12.3
Selected demographic and clinical characteristics of all participants	Mean ± SD	
Duration from diagnosis in months (n=178)	64 (12.8, 140)*	
Age (years) (n=179)	44.7 ± 15.1	
Duration of symptoms (in weeks) (n=161) *	169 (79 -392)*	
Weight in(kg) (n=162)	62.3 ± 23.7	
Tender Joint Count (n=179)	2.0 ± 4.1	
Swollen Join Count (n=179)	2.1 ± 4.2	
Patient assessment of disease activity using VAS (n=178)	4.6 ± 2.6	

* *Median (IQR*

The most common constitutional feature was morning stiffness found in 99 patients (55.3%) and fever found in 41 (22.9%). Few had nodal disease 7 (3.9%). The mean age was 44.7 (SD15.1), with mean disease duration of 64 (12.8-140) weeks. Duration from onset of symptoms till diagnosis was 169 weeks (79- 392).

The average Tender Joint (TJC) and Swollen Joint Counts (SJC) were 2.0 (SD±4.1) and 2.1 (SD±4.2) respectively. The mean Visual Analogue Score (VAS) for pain was 4.6 (SD±2.6). Rheumatoid factor was positive in 78 (43.6%) and ACPA was positive in 100 (55.9%).

Majority, 145/179 (81%) were on steroids (both oral/injectable) with 96 (53.6%) on methotrexate. One hundred and nine (60.9%) were on hematinic and 102 (57.0%) on hydroxychloroquine. The distribution of other medications is as shown in Table 2.

Table 2: Antibody profile and medications of rheumatoid arthritis patients

Laboratory	No.	(%)
Rheumatoid factor	78	43.6
Antinuclear antibodies	14	7.8
Anti Double-Stranded DNA	1	0.5
Extractable Nuclear Antigens	2	1.1
Ab to ENA - Scl-70	1	0.5
Ab to ENA - Ro(SS-A)	3	1.7
Ab to ENA - La(SS-B)	2	1.1
Ab to ENA - RNP	4	2.2
Anti-citrullinated protein/ peptide antibodies	100	55.9
High ESR(n=137)	115	83.9
High CRP(n=42)	17	40.5
Low Hemoglobin(n=142)	58	40.8
Low Total Protein(n=111)	97	87.4
Low Albumin(n=135)	25	18.5
Drugs		
Steroids(oral/injectable)	145	81.0
Hematinics	109	60.9
Proton pump inhibitors	103	57.5
Hydroxychloroquine	102	56.9
Methotrexate	96	53.6
ACE-Inhibitors	30	16.8
Sulfasalazine	24	13.4
NSAIDS	14	7.8
Azathioprine	11	6.1

**Multiple response analysis*

The site of joint involvement was not significantly associated with high ESR levels, though individuals with high ESR had 10% increased odds (cOR=1.1 95%CI=0.4–3.2) of having generalized joint involvement compared with those without evidence of synovitis in the joints.

Sex and site of joint involved were not significantly associated with high VAS independently. Higher proportion of females had high VAS compared to males (89.3% vs 10.7%) and individuals with generalized joint involvement also had a higher VAS compared to individuals with no evidence of synovitis, small or large joint involvement (60.7%, 7.1%,7.1% and 25% respectively).

Discussion

This study reports on 179 RA patients seen over a two-year period. Whilst this was not a prevalence study, it demonstrates similar trend of increasing reports from sub Saharan Africa. Females formed the majority of patients in our cohort accounting for 82.1% of those affected, with a female: male ratio of 4.59:1 similar to what has been reported in other African countries (Table 1). Female to male ratio seems to vary across countries, in 1995, female to male ratios in different African countries were similar to that of European whites (F/M ratio from 1.5:1 in Nigeria ranging to 3.7:1 in South Africa, compared to 2-4:1 in Europe)[8]. An Egyptian cohort showed a ratio of 6.7:1[9]. In Europe, a recent study in the United Kingdom found a female: male ratio of 2.64:1[10].

The age of Ghanaians with RA (41.4 years) is closer to that reported in Europeans/Caucasians compared to that of Africans populations. The mean age of onset has been found to be consistently lower in Africans compared to Caucasians (36 years in Africans compared to 44 years in Caucasians). This may be due to socioeconomic factors and differences in life expectancy[11]. The elderly population is significantly less in African countries, which will presumptively decrease the mean age of diagnosis, as fewer people live long enough to experience "late-onset" RA.

Morning stiffness >1 hour was experienced by 55% of our patients. Nearly 90% of people with active RA experience morning stiffness, according to a 2014 review in the journal BioMed Central Musculoskeletal Disorders[12]. It is possible therefore a low prevalence of morning stiffness may lead to under diagnosis of RA in Ghana.

Fatigue was experienced by a small minority (14%) of our patients in keeping with the observation that this symptom is underrepresented in developing countries[13]. These dual observations suggest that a proportion of cases of RA in Ghanaians reside in the milder spectrum of disease. This notion is supported by the relatively low tender and swollen joint counts (2) and RA nodules (7/179).

Nodules are usually a sign of advanced RA and are also more common in anti CCP and Rheumatoid factor positive patients as well as those who smoke[14-16]. Our research involves a young cohort with short disease duration and only 43.6% were RF positive and 55.86% being ACPA positive. RA has been said to be milder in Africans from studies in Nigeria, South Africa, Zimbabwe, Congo-with fewer extra-articular features, less subcutaneous nodule formation, younger age of onset and less radiological damage compared to Caucasians and other black populations from elsewhere[17-21]. However more recent studies suggest that RA is likely than previously thought,

to be more common and be more severe in the black races of sub Saharan Africa[22-24].

In African populations the diagnostic value of ACPA remains secure despite the finding of low numbers of the Shared Epitope (SE) and low numbers of smokers, signifying that other factors may influence ACPA positivity in Africans (37). However the specificity of IGM RF as a diagnostic tool is diminished due to the high percentage of positive tests in a population with a the high background of chronic infection.

Early diagnosis and treatment influence disease outcome in RA with a window of opportunity in the region of 3-6 months only to commence effective treatment. Adverse outcomes are likely when this target is not achieved.

Duration from onset of symptoms to diagnosis was 169 weeks (approximately 39 months) in this Ghanaian cohort. This prolonged delay in diagnosis of RA is a feature of many African studies. This reality reflects an educational gap about the disease among health care providers, a gross scarcity of rheumatologists and the fact that many patients resort to alternative health care providers before seeking a medical opinion[24].

The patients in our study were mainly from a middle income group treated with standard DMARDs. In many African nations, medication cost and monitoring may limit access to DMARDs leading to delayed presentation and adverse outcomes for some. Moreover the pervasive use of steroids (as in our cohort) may result in the amelioration of symptoms, leading to long lag time to diagnosis and referral[24].

This study was limited by the fact that the data was retrospective leading to some missing values. We could not calculate activity scores e.g. DAS 28 or determine radiological scores eg Sharp score which would have provided more detailed information about disease activity and disability.

Conclusion

In this first study of RA in Ghanaians, the key findings were similarities between our patients and other West African populations in age, sex and joint distribution, a relatively low joint count, few extraarticular manifestations and little nodal disease. More studies need to be conducted to estimate the true burden and patterns of RA in Africans so that appropriate health policies can be implemented.

Declarations

Ethical approval: Ethics approval was not required at the time data set was collected for retrospective studies.

Data: Data and materials are available on request.

Authors' contributions: All authors who contributed to this research have been acknowledged.

Conflict of interest: The authors have no competing or conflict of interest to report.

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Case report

A misleading appearance of a common disease: A unique presentation of extra pulmonary and multifocal tuberculosis: case report and literature review

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Abstract

Tuberculosis (TB) continues to be a common cause of infectious disease, and it's a common illness for vulnerable populations in resource-limited settings**.** Extra Pulmonary Tuberculosis (EPTB) accounts for about 20% of TB cases worldwide. Until now, the diagnostic of ETB is not initially considered especially in the setting of a vague clinical presentation, particularly when it is a multifocal localization defined as the presence of lesions, affecting at least two extrapulmonary sites, with or without pulmonary involvement. Elsewhere multifocal forms are exceptional even in endemic countries and affect mainly immunocompromised patients. Here, we report an uncommon case of extra pulmonary and multifocal tuberculosis, with vertebral, digestive and lymph node involvement in a young immunocompetent patient. Diagnosis was confirmed by pathology after the surgery.

Key words: Tuberculosis, Extra pulmonary, Spine, Infection, Bone

Introduction

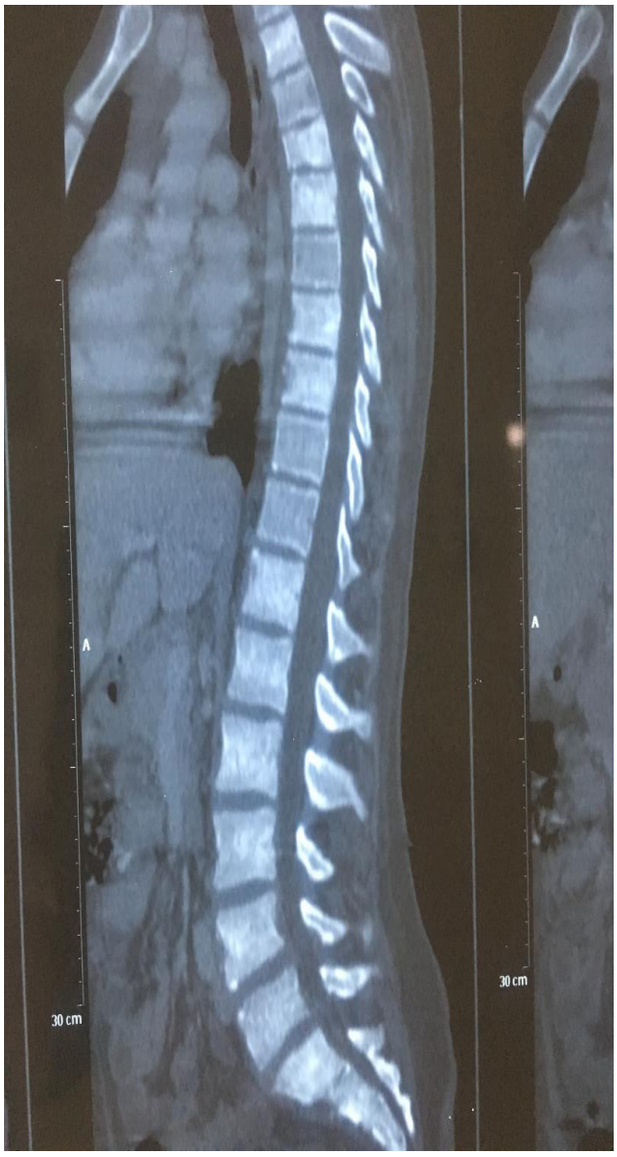
Tuberculosis (TB) continues to be a common cause of infectious disease afflicting up to one-third of the world's population[1]. An estimated 1.67 million people died from TB in 2016[2]. Africa accounts for 3 in 10 cases of TB worldwide and about 4 in 10 cases of TB mortality globally[3]. The causative organism *Mycobacterium tuberculosis*, which is predominantly air-borne, affects the lung causing pulmonary TB. When TB is bacteriologically confirmed or clinically diagnosed in other parts of the body other than the lung such as the abdomen, meninges, genitourinary tract, joints, bones, lymph nodes and skin it is classified as EPTB. Various risk factors reported to be associated with EPTB include immunosuppression, HIV infection, male gender and younger age[4]. On the other hand, other studies have found females and increasing age to be more associated with EPTB[4].

Despite all technological advances, the diagnosis of tuberculous spondylitis remains a clinical challenge since it depends on a high grade of clinical suspicion. This case report shows the importance of taking into consideration a possible TB aetiology even when lesions are observed far away.

Case report

A 16-year-old Algerian man, presented with a 3 month history of permanent lower lumbar pain without radicular distribution. He had a history of asthenia with weight loss of 20kg over the past 12 months with fever, and diarrhoea. He had a colonoscopy which showed segmental areas of inflammation in ileum, pathology showed severe lymphoplasmacytic infiltration, marked architectural distortion, and chronic inflammation without granulomas. The patient was diagnosed with Crohn's disease and was treated with prednisone and mesalazine. However, his symptoms progressively worsened over the next three months, with installation of low back pain. At the physical examination, he had showed good general state of health, tenderness over the lumbar spine without limitation, and no neurological signs. Heart and lung auscultation were normal with no hepatosplenomegaly or adenomegalies. Laboratory findings showed a normocytic and normochromic anaemia (haemoglobin 8.7 g/dL), and thrombocytosis (platelets: 618 x 10^9/L). C-reactive protein levels of 26.9 mg/dL and an erythrocyte sedimentation rate of 81 mm/h. The tuberculin test was phlyctenular. Computed Tomography (CT) of the thorax, abdomen and pelvic (Figure 1) revealed deep abdominal lymphadenopathy, with ostéomyelitis ivory in appearance at multiple dorsal-lumbar and sacral vertebrae contiguous and noncontiguous.

Figure 1: Computed Tomography: ostéomyelitis ivory in appearance at multiple dorsal-lumbar and sacral vertebrae contiguous and noncontiguous



Histopathological examination of spine bone biopsy and ileum revealed granulomatous lesions with caseous material and multinucleated giant epithelioid cells in favor of spinal tuberculosis. The diagnosis of Crohn's disease was no longer considered and removed from his medical history but considered intestinal tuberculosis. At his last clinic visit, six months into his treatment without any complaints, the treatment will be maintained for 12 months.

Discussion

Despite being a curable disease, TB remains a major public health problem worldwide and one of the diseases with higher mortality. Ohene *et al*.[4] reported that proportion of EPTB among TB patients was 21.8%, fell within the range of what has been reported for other countries such as Swaziland (18.4%), Cameroon (19.4%) and Botswana (25%).

The proportion of EPTB varies from region to region, reflecting HIV prevalence such as Benin, with a low HIV prevalence (1%) compared to Botswana, which reported an EPTB prevalence of 9%, and in Tanzania EPTB accounted for 15% in one study, and amongst them 58.3% were HIV positive[5-7]. Despite the low rate of HIV infection in north of Africa, EPTB rates are even higher in this countries with Morocco and Algeria reporting 44.4% and 60% respectively, and 56.9% in Tunisia[8]. Female gender, socio-demographic data, and younger patients represents a major risk factor for EPTB according to several published reports in Turkey, USA, Asia, Egypt and North Africa[8-12].

Multifocal TB is characterized by the presence of large multifocal tuberculous areas in the same or different organs. On the other hand, disseminated haematogenous TB is characterized by the presence of large numbers of tubercle bacilli throughout body sites, resulting in large numbers of tiny tubercular lesions (1-3 mm in diameter). This entity is usually referred to as miliary TB and has a variable clinical presentation[13].

Multifocal skeletal TB is defined as osteoarticular lesions that occur simultaneously in two or more locations, with or without pulmonary involvement. It is uncommon, with a reported incidence of 7–10%, and is usually associated with disseminated disease[14]. Multifocal intestinal TB is less defined and may refer to multiple liver lesions in the presence of miliary TB. Multifocal systemic TB may merely be referred to as multifocal TB[13]. The term multifocal systemic disease is preferable, because the entity is characterized by the presence of two or more lesions in extra-pulmonary sites, with or without pulmonary involvement.

As in this case described, it is often difficult to promptly diagnose multifocal systemic tuberculosis. Of importance, diagnostic delay, often linked to non-specific symptoms, can have a significant impact on disease progression, favoring the spread of TB to other organs or the impairment of organs already affected by TB. The most common presenting complaint of spinal TB is back pain[15].

Our patient presented two atypical features which delayed the diagnosis, the first one is the intestinal tuberculosis which has been confused with Crohn's disease. The second one is the bone tuberculosis with uncommon contiguous and noncontiguous spinal tuberculosis with ivory aspect.

The intestinal tuberculosis is rare in developed countries and accounts for less than 1% of all cases of abdominal tuberculosis[16]. However, its prevalence is significantly higher in countries where tuberculosis is endemic, such as India, African, and Southeast Asia.

However the intestinal tuberculosis and Crohn's disease, frequently present with similar clinical symptoms of weight loss, abdominal pain, fever, bowel obstruction, and bloody diarrhoea, endoscopic findings of skip lesions, ulcerations, and terminal ileum involvement and pathological features, it is occasionally difficult to distinguish between them, thus resulting in a misdiagnosis

as described in our clinical case[17]. The histologic hallmark of intestinal tuberculosis that best distinguishes it from Crohn's disease is confluent caseating granulomas, within the submucosa with positive acid-fast bacilli staining.

Vertebral involvement is also particular in our case, because usually, two or more contiguous vertebrae are involved in spinal tuberculosis owing to haematogenous spread through one intervertebral artery feeding two adjacent vertebrae[18] and despite the typical presentation of spinal TB, multiple atypical features have been reported in the literature[19]. These formes are indistinguishable from metastasis or lymphoma.

The characteristics uncommon in children with atypical spinal TB include the lack of atypical spinal TB are mainly involvement of the posterior elements of the vertebrae, no intervertebral disc involvement, and extradural spinal cord compression without bony involvement, and the association of multifocal systemic tuberculosis and spondylitis is uncommon in children[20].

Our patient had the tuberculous involvement in almost all spinal levels. There were multiple contiguous and noncontiguous lesions in thoracic, thoracolumbar, lumbar and sacral vertebrae without paravertebral abscesses, and without primary lung tuberculosis infection. What was interesting in our patient was the condensing aspect with ivory aspect of the vertebrae instead of a rather lytic aspect. While the condensing aspect giving the ivory aspect of the vertebrae secondary to tuberculosis is found in 10% [21].

In this patient the source of infection was probably the intestinal infection, since the chest scanner was revealed without anomalies. Turgut[22] put forward pelvic infection as a source of spinal tuberculosis in his patient and Kulali *et al*.[18] reported that they could not find any source in their patient. Other multifocal noncontiguous spinal tuberculosis cases in the literature are the cases in small series, and we could not reach any information about their infection sources.

Wang *et al*[19] reported eight patients with single noncontiguous, multi-segmental, atypical spinal TB with no intervertebral disc involvement. To our knowledge, no case similar to ours has been described, to know a multifocal systemic tuberculosis combining a deceptive intestinal and vertebral form with lymph node involvement without pulmonary involvement. The goal of multifocal systemic tuberculous treatment is to eradicate infection and to treat and prevent different complications as neurological complications or spinal deformities. Pharmaco-logical treatment should be initiated as soon as the diagnosis is confirmed, with 2 months of HRZE (intensive phase) followed by 4 to 7 months of HR (continuation phase). The duration of treatment remains controversial. Due to difficulties in assessing response and risk of relapse, most experts recommend 9 to 12 months of treatment, and in situations of slow radiological resolution as case 2, 12 to 24 months of treatment should be considered[23].

Conclusion

TB may cleverly mimic many diseases and affect multiple organ systems and sites. Thus a high level of suspicion for TB should be maintained in patients with multiple sites of involvement, especially in countries where TB is endemic.

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Case report

Osteoid osteoma of the patella simulating knee arthritis: case report

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Abstract

Osteoid Osteoma (OO) is an uncommon benign tumour and causes severe pain, being worse at night, and it responds dramatically to nonsteroidal anti-inflammatory medications. An osteoid osteoma of the patella is very rare and if it arises, close to chondral surface differential diagnosis may be challenging. Patients with OO of the patella often present with knee pain that is also a typical symptom of trauma or of other diseases such as arthritis, which are much more common than OO. We present the case of a 19-year-old woman, basket-ball-player, with a three year history of intense Anterior Knee Pain (AKP) that was first attributed to arthritis. A CT scan was performed that revealed the localization of an osteoid osteoma of the patella. The patient was successfully treated with open surgical technique, and the diagnosis was confirmed after histopathologic analysis. After one year of treatment, there was no relapse of the pain and no residual recurrent tumour. This unusual location was at the origin of unexplained pain and delayed diagnosis made so later. Although a rare entity, OO of the patella with its atypical clinical features could be included in the differential diagnosis of persistent anterior knee pain in the young adult. High clinical suspicion is necessary to avoid delay in diagnosis and irrelevant procedures for the patient.

Key words: Osteoid osteoma, Knee pain, Intra-articular, Patella, Tumour resection

Introduction

Osteoid Osteoma (OO) is a benign osteoblastic tumour (11% to 14% of all benign bone tumours)[1] described by Jaffé in 1935[2], that occurs mostly in children[3] and young adults, affecting men twice as often as women. History of nocturnally aggravating and salicylate-responding pain is characteristic for this tumour. The lesion is commonly found on the diaphysis or metaphysis of long bones, and its typical radiological appearance is a radiolucent zone surrounded by sclerotic bone (nidus) smaller than 1.5cm in diameter[1]. Pathologically, variable osteoid tissue and immature bone trabeculation are observed in vascular mesenchymal tissue. As a rule, reactive bone is more vascularized than normal bone, and the periost, which takes place on it, become thick. Although the lesion is seen in fibula, humerus, vertebra, talus, and calcaneus at times, it is frequently located in femur and tibia[4].

Intra- and juxta-articular OO are a diagnostic challenge for the physician, due to their rare appearance (13% of the lesions) and also their atypical clinical and radiological characteristics[5]. Misdiagnosis and delay till definitive treatment is a common problem, especially when the lesions arise in a subchondral location in the knee or the patellofemoral joint[6].

We present the case of a patellar OO in a young woman that was treated by surgical ablation. The uncommon site in combination with the atypical clinical presentation caused 3 years interval between the onset of the symptoms and final treatment, especially since the initial MRI did not identify the lesion, unlike scintigraphy and computed tomography in millimeter sections.

The difficulties a clinician faces, in his effort to diagnose a rare entity presenting with a vague knee symptomatology and thus focus on crucial points in the diagnosis of intra- and juxta-articular OO, should be highlighted. The aim of this study is to report this rare case of patellar OO simulating knee arthritis along with a review of the literature.

Case report

A 19-year-old woman, presented to our institution with a three-year history of pain in her left anterior knee pain, that was predominantly nocturnal and sensitive to nonsteroidal anti-inflammatory drugs and attributed to a direct blow on the patella he had sustained during training. Later, a warm increase in the left knee was reported describing mono-arthritis, with knee Magnetic Reasoning Imaging

(MRI) showing an important inflammatory reaction with edema which could evoke an infectious focus. The patient treated as septic arthritis, seeing the absence of germs in the analysis of synovial fluid and the inefficiency of antibiotics, the diagnosis of spondyloarthritis was made and the patient was treated with sulfasalazine and then biotherapy without any clinical improvement. A clinical examination showed lameness while walking and swollen knee, hot and very painful to palpation, without patellar shock. This pain was aggravated by kneecap pressure and mobilization. Bending was limited to 90°. There was no quadricipital amyotrophy.

An X-ray of the knee had been obtained with unremarkable findings outside of a sub-patellar soft tissue densification with a left patella side flip. At the joint ultrasound, there was a sequellary inflammation of Hoffa's grease with involvement of the patellar fin and a pre-patellar bursopathy. A second MRI of the left knee with perfusion imaging, supplemented by Computed Tomography (CT) (Figures 1 - 2), objectified osteoid osteoma under lower cortical patellar crest. Bone scintigraphy (Figure 3) shows an aspect compatible with an active osteoblast transformation at the left patellar level, evoking osteoid osteoma in the first place.

Figure 1: Axial CT scans show a round, well-marginated sclerotic lesion with a hypodense rim and a centrally calcified nidus

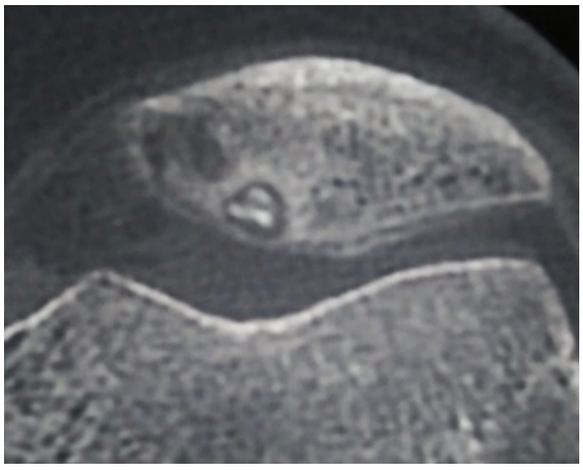
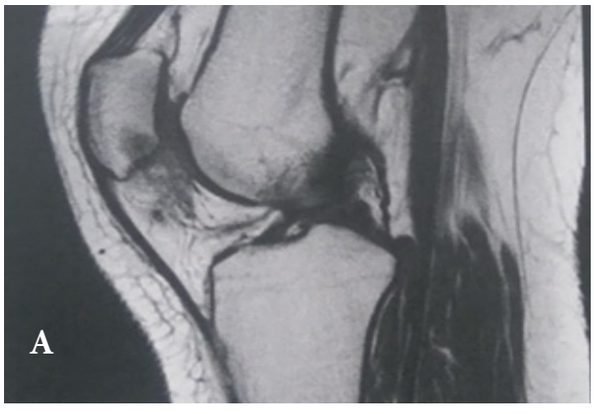


Figure 2: stratified aspect achieving a target aspect, with a center in hypo signal T1 (a) and T2 (b) that increases intensely after contrast, corresponding to a nidus



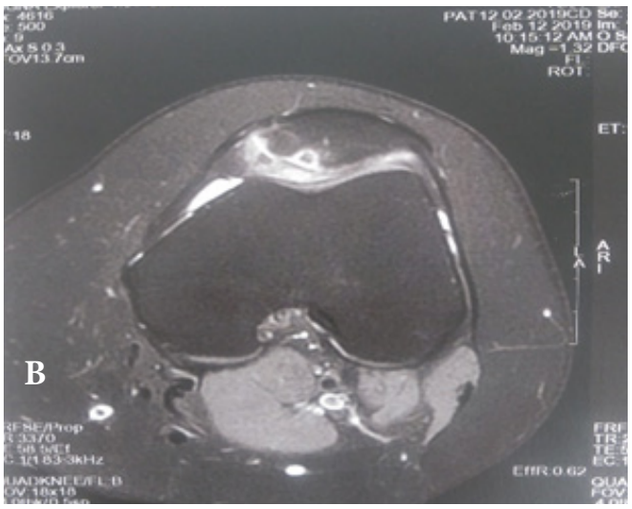
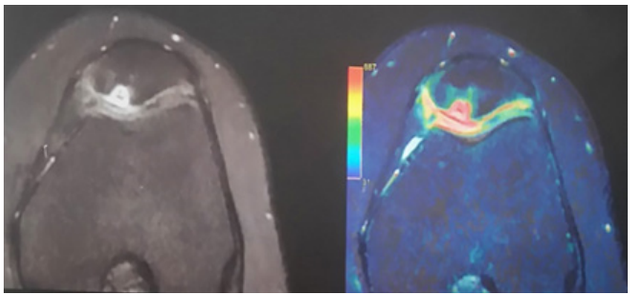


Figure 3: MRI T2 with bone perfusion shows the presence of a central tumour blush corresponding to a nidus with early intense contrast taken parallel to arterial contrast taken with early and intense WASH IN



The patient had a surgical removal of the tumour, with good surgical follow-up. The anatomo-pathological examination of the operative room confirms the diagnosis. Currently, at one year in post-operative, the patient is totally asymptomatic, with total resumption of mobility of the left knee.

Discussion

Osteoid Osteoma (OO) is a benign and painful skeletal tumour. It occurs mainly in children and young adults with 90% of cases seen before the age of 25 years and a male/female ratio of more than 2:1[7]. OO can occur everywhere in the skeleton both in the cortex and medulla[7].

Intra-articular OO accounts for approximately 10% of all osteoid osteomas and mainly arises in the elbow, the ankle or in the hip joints[8], and 2.5% of all paediatric lesions. Patellar OO is rare and only few cases are described in the literature[8]. It is a difficult lesion to diagnose, with misdiagnosis being very common and a resulting delay between the onset of symptoms and appropriate treatment, especially around the knee joint the diagnosis can be delayed for many months[6]. In our case, the interval between the first symptoms and diagnosis was 3 years.

The most common symptom when an OO arises around the knee joint is AKP. However, AKP is one of the most frequently met musculoskeletal disorders. Synovitis, stiffness or swelling of the soft parts and reduced joint

mobility are rare clinical manifestations. Each year many young athletes seen in primary care setting complain of some degree of knee pain, which is usually attributed to chondromalacia patella, patellar tendinitis, mediopatellar plica syndrome, Hoffa's syndrome, patellofemoral malalignment, osteochondritis dissecans, meniscal tears, or ligamentous injuries[9]. The pain encountered from an OO is the result of the high prostaglandin levels produced within the nidus[10]. The transmission of these prostaglandins from the nidus to synovium causes lymphofollicular synovitis, resembling histologically rheumatoid arthritis and clinically monoarthritis of infectious, degenerative, or rheumatologic origin. The diffuse pain due to synovitis and the lesion itself accompanied by non-specific symptoms as muscle atrophy or muscle spasm around the joint, limited range of motion, joint effusion and swelling, gait and postural disturbances may be misleading for the clinician[11].

Szendroi *et al*.[12] compared diagnostic delays between OO and other localizations. The average time for intraarticular osteomas was 26.6 months, compared to 8.5 months for other locations. The radiological features of intraarticular osteomas are as many traps. The classic image of nidus, bordered by peripheral ostesclerosis is most often absent (50-75%). Conventional radiology is either normal or characterized by local periarticular osteopenia. The conventional radiological diagnosis of patellar OO is diffcult due to the absence of periosteal reaction[13].

Standard radiographs only provide subtle findings due to the absence of any perilesional sclerosis or periosteal reaction, unlike extra-articular locations. According to some authors, MRI remains the modality of choice for bone tumour exploration. On MR imaging, OO typically shows low signal intensity on T1 and T2-weighted images with bone marrow edema depicted around the nidus and high contrast enhancement after gadolinium administration. Intra-articular lesions may demonstrate synovial thickening apparent on MRIs, diagnosis being confirmed after gadolinium injection. However, precise localization of the nidus may not be easy. In 35% of the cases, the nidus cannot be detected since it is often hidden by the associated peri-lesional edema surrounding the lesion while in 50% of the cases, the nidus has an atypical presentation, which may lead to misdiagnosis. Our patient had to have two MRI's and a CT scan to make the diagnosis, because symptomatology was in reality misleading to be able to steer the diagnosis.

Bone scintigraphy is highly sensitive but demonstrates a lower specificity than CT scan particularly in case of intra-articular location because bone sclerosis around the nidus cannot be detected early since there is a less intense uptake due to the associated synovial reaction[14]. In the treatment of OO within this area; open curettage and excision of the nidus with minimal bone loss and without damaging the articular cartilage, and if technical opportunities are sufficient, percutaneous nidus excision radiofrequency ablation using CT or three-dimensional navigation system can be applied[4.] Our patient has been treated by surgical ablation with total healing.

Conclusion

Osteoid joint osteoma of the knee is a difficult lesion to diagnose. Clinical presentation is most often atypical. Errors of assessment are frequent, which make the bed to many inappropriate therapeutic procedures. Confrontation of the clinic and several imaging means is often necessary. Treatment should avoid causing cartilage damage. Percutaneous surgery is the reference technique for treating these lesions.

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Infective endocarditis is a potential differential diagnosis of systemic lupus erythematosus: case report

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Abstract

Background: Systemic Lupus Erythematosus (SLE) is multisystemic autoimmune chronic inflammatory disease. It has a relapsing remitting course. Here, we present a male patient with SLE who presented with signs and symptoms mimicking sub-acute infective endocarditis.

Case report: A 28 year old male presented with fatigue, fever, arthritis, and anaemia. He had past history of oral ulcers. Antinuclear antibody ANA was positive. Diagnosis of SLE depending on 2012 SLICC SLE criteria[1] was done and methylprednisolone IV pulse therapy was given for 3 days. On the 4th day he developed chest pain for which echocardiography was done and showed vegetation. Because of suspicion of infective endocarditis IE which cannot be excluded at that time, IV antibiotics were started. Blood culture was negative, it can be negative in 2% to 40% of IE patients, so antibiotics were continued for 4 weeks. Echocardiography repeated at the end of 4th week revealed no vegetation. The patient was discharged and was asked to come back for follow up and to repeat ANA and anti-dsDNA antibodies. At the 5th week, the patient came with active arthritis, fatigue, discoid rash and vasculitic body rash. ANA was repeated and found to be highly positive 1:10240. A final diagnosis was SLE associated with Libman Sacks endocarditis.

Conclusion: Infective endocarditis shared a lot of signs and symptoms of SLE. Antinuclear antibodies are also positive in infective endocarditis and this makes some diagnostic difficulties.

Key words: Systemic lupus erythematosus, Libman Sacks endocarditis, Infective endocarditis

Introduction

Systemic Lupus Erythematosus (SLE) is multisystemic autoimmune chronic inflammatory disease. It has a relapsing remitting course. Symptoms vary between people and may be mild to severe[2]. Common symptoms include painful and swollen joints, fever, chest pain, hair loss, mouth ulcers, swollen lymph nodes, feeling tired and a red rash which is most commonly on the face[2].

Infective Endocarditis (IE) is infection of the endocardium, usually with bacteria (commonly streptococci) or fungi. Common signs and symptoms include fever, heart murmurs, petechiae, anemia, embolic phenomena, and endocardial vegetations. The Duke diagnostic criteria, developed by Durack and colleagues[3], are generally used to make a definitive diagnosis of IE.

Here, we present a male patient with SLE who presented with signs and symptoms mimicking sub-acute infective endocarditis.

Case report

A 28 year old black man from south of Libya presented to rheumatology out patients clinic complaining of general weakness, fatigue, fever, and arthralgia for the last two months. He had past history of recurrent mouth ulcers. Clinically he was pale and febrile (temp. 39.5°C). He had rounded hypopigmented lesion on scalp behind the left ear and small vasculitic rash on the upper chest. He had both wrist joints arthritis. Heart examination revealed systolic murmur at the mitral area. Investigation showed haemoglobin of 8.7 g/dl, ESR was 85 mm/hr, coomb's test was negative. ANA which was done by ELISA test in local laboratory was positive. So, a diagnosis of SLE depending on 2012 SLICC SLE criteria[1] was done and IV methylpredisolone pulse therapy 1gm daily for 3 days was given.

On the 4th day, he presented for follow up, he showed signs of improvement, no more fever, no active arthritis. But he had sharp chest pain, echocardiography was requested which showed heterogeneous echo density, irregular border partially mobile vegetation started from sino tubular junction to ascending aorta which was confirmed by transesophageal echocardiography (Figures 1, 2).

Figure 1: Transesophageal echocardiography showing vegetation at ascending aorta

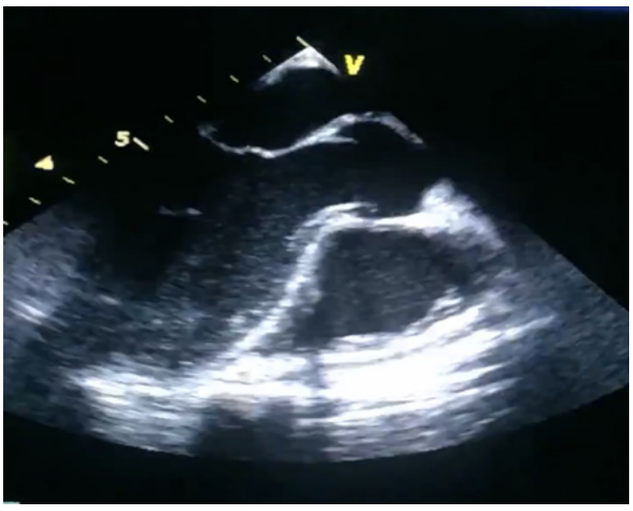
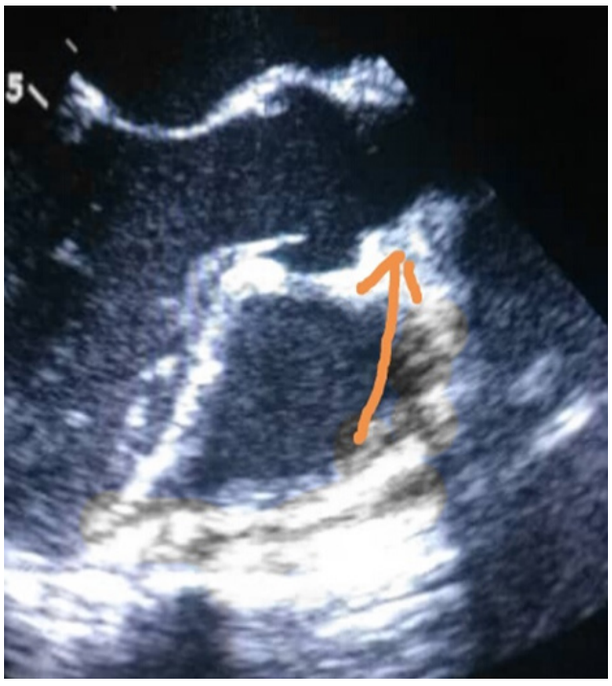


Figure 2: Arrowhead, heterogeneous echo density, irregular border vegetation started from sino tubular junction to ascending aorta



The patient was admitted to cardiology department as a case of infective endocarditis and treated by IV antibiotics for 4 weeks. Two blood cultures were negative. Echocardiography repeated at the end of the 4th week revealed no vegetation. The patient was discharged and was asked to come for follow up and to repeat ANA and anti-dsDNA antibodies. After one week, the patient presented with recurrence of fatigue, both wrist arthritis, skin rash and active discoid rash on the scalp. ANA was positive with high titer (1:10240), fine speckled pattern. Anti-dsDNA was negative. CBC revealed normocytic normochromic anaemia and high ESR (64mm/hr). Prednisolone 60mg daily and hydroxychloroquin 200mg twice a day were started. The patient is now doing well, he is in remission on prednisolone 5mg daily and hydroxychloroquin 200mg twice a day.

Discussion

Lupus symptoms are also symptoms of many other diseases and this sometimes makes diagnostic difficulties. A common shared feature between infective endocarditis and lupus are skin rash, fever, anaemia, arthritis and positive ANA (Table 1).

Table 1: Clinical features of IE versus SLE with LSE

Clinical feature	IE	SLE with LSE
Fatigue	+	+
Fever	+ rarely exceed 39.4°C	+ rarely exceed 38.89°C
Skin rash	+	+
Arthritis	+	+
Valvular dysfunction (murmur)	+ present in >85%	+ present in only 20%
Normocytic nomochromic anaemia	+	+ and can be macrocytic due to comb's positive haemolytic anaemia
Blood culture	+ positive	-negative
Echocardiography (vegetation)	+	+
ANA at diagnosis	Can be positive in 8% -30%	Positive in 98%
ANA after antibiotics	Become negative	Remain positive
Other features (thromboembolic)	+	+ and also clinical features of SLE

Fever in lupus is usually low-grade, rarely exceeding 38.89°C. A temperature greater than this should stimulate a search for an infection as the source of fever[4]. This patient had a fever of 39.5°C which made an infection (IE) on top of differential diagnosis. But fever is a common manifestation of SLE and can occur in 36-86% of patients[5,6]. Blood culture of this patient was repeated twice and both results were negative. Blood cultures are negative in 2% to 40% of infective endocarditis patients, with some studies reporting blood culture-negative rates of up to 71% [7-11].

ANA is positive in 98% of SLE patients and the usual ANA pattern in SLE is homogenous and fine speckled patterns. ANA is also positive in infective endocarditis in 8% to 30% of patients, with a titer as high as 1:640. But positive ANA test results revert to negative after antibiotics therapy[12-16].

In our patient, ANA was positive from beginning and when repeated after antibiotic treatment, it was highly positive (1:10240), the pattern was fine speckled and this supported a diagnosis of SLE with heart involvement (Libman sacks endocarditis).

Libman Sacks (LS) endocarditis LSE is a form of nonbacterial endocarditis that is seen in association with SLE. It is one of the most common heart related manifestations of lupus (the most common being pericarditis)[17]. It was first described by Emanuel Libman and Benjamin sacks at Mount Sinai Hospital in New York City in 1924[18,19]. Libman sacks endocarditis most commonly affects mitral and aortic valves, but other valves may be involved[18,19]. LS vegetations comprise immune complexes, mononuclear cells, fibrin, and platelet thrombi. It can be complicated by embolic cerebrovascular disease, peripheral arterial embolism, and by superimposed infective endocarditis. It is also associated with increased mortality[20]. There are laboratory tests to confirm the diagnosis of LSE[21]. However, the primary evaluation for LSE is by echocardiography. Trans-esophageal echocardiography has greater sensitivity and specificity than trans-thoracic echocardiography[21].

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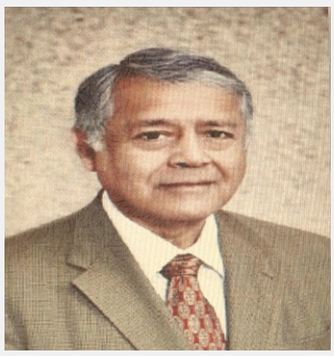
Prof. Luis Rolan Espinoza: My tribute



I received the news of passing of Prof. Luis Rolan Espinoza (MD, MCP, MACR) with total shock and disbelief, and it is with deep sorrow that I write this tribute. Prof. Espinoza was until his death the head of Rheumatology Unit in Louisiana State University. He was also the President of the PANLAR congress which was scheduled to be held in Miami later this year.

For Prof. Espinoza and I, it has been indeed a long journey. While studying international health at Tulane University and Rheumatology at Louisiana State University in the United States of America in 2004, Prof Espinoza was not only my teacher and mentor but my host and father figure too. We worked together and managed to accomplish lots of stuff. He was the actual strength beneath my feet and taught me what it takes to be a great rheumatologist. He always pushed me really hard to write. Together with him I managed to publish articles in various international journals[1-5]. He further recruited me to be a member of the editorial board of *Clinical Rheumatology Journal* when he was the Editor in Chief. Every time Prof. Espinoza was a guest editor of any book or journal he always invited me to make contributions, some of which were published by Springer Publishers[6]. When we established the *African Journal of Rheumatology*, (AJR) in 2013, he accepted our invitation to become an editorial advisor and wrote an editorial for the third issue of the journal[7]. Since then, he remained one of the main reviewers for the journal. Through him and with his inspiration and support, together with other senior colleagues from the African continent, I was later privileged to be the President of AFLAR and subsequently, President of ILAR. I can therefore confidently state that working closely with him shaped my growth and attitude which have greatly contributed to my professional development.

While visiting Kenya as an ILAR scholar in the year 2005, Prof. Espinoza together with his wife and daughter who are both doctors (Carmen a dermatopathologist and Gabriella an ophthalmologist), managed to visit the Nairobi Hospital, the Aga Khan University Hospital and Kenyatta National Hospital where he gave lectures on various topics in rheumatology. Carmen had a busy engagement with our local pathologists while Gabriella was interacting with the ophthalmologists. They also had time to go on safari to the beautiful Maasai Mara game reserve. Through that visit, the bond between us grew even more.

Prof. Espinoza was a unique figure among the distinguished rheumatologists. Sharply perceptive, meticulously thorough and elegantly articulate. He was friendly, personable, unassuming, and a modest individual, a man I admired greatly. One cannot help to be saddened by the departure of this great physician, a towering rheumatologist and a friend. His commitment to rheumatology; humility, politeness and unassuming nature was not only amazing but also inspiring. His sudden demise has left me speechless. May his contribution to the world of rheumatology; lifetime achievements and his towering voice walk with us and be an inspiration to the new generation of rheumatologists. R.I.P. my friend and mentor Prof. Luis Rolan Espinoza (MD, MCP, MACR).

For we know that if the earthly tent we live in is destroyed, we have a building from God, an eternal house in heaven, not built by human hands"
1 Corinthians 5:1

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All manuscripts are blind peer reviewed to ensure that published work is of high quality and would add to the existing knowledge in the field of rheumatism and arthritis. Acceptance for each manuscript is on the basis of its originality, clarity of presentation and use of relevant references. A manuscript is usually subjected to several reviews and resubmissions before it is eventually accepted for publication or rejected. Authors submit articles on the understanding that the work submitted has not been submitted to another journal. Authors must indicate this when submitting manuscripts. The journal's policy is to communicate to the authors the verdict of the reviewers within three months from the date of manuscript submission.

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The journal uses the Vancouver style. References should be numbered in order of appearance and only those cited should appear in the reference list.
Abbreviations and acronyms should be defined the first time they are used; for example, the Kenyatta National Hospital (KNH).

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