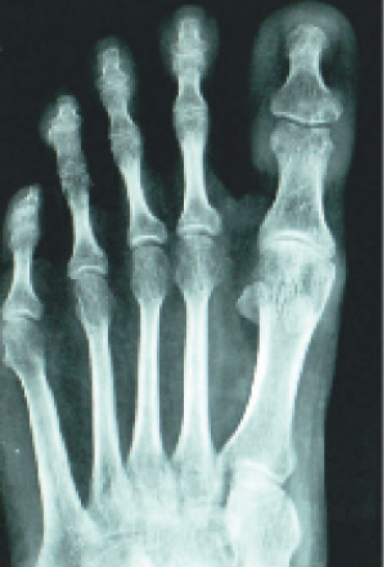

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CONTENTS

EDITORIAL

46. Glucocorticoid induced osteoporosis – is it relevant in Africa?
Kalla AA, Hmamouchi I, Paruk F, Tabra S, Maatallah K

REVIEW ARTICLE

50. Covid-19 vaccination in rheumatic diseases: an overview
Omondi C

RESEARCH ARTICLES

53. Prevalence of neuropathic pain in patients with common low back pain with radiculalgia in sub Saharan Africa: a bicentric cross-sectional study of about 409 patients
Kaboré F, Diomandé M, Tiendrébéogo WJS, Ouattara B, Sougué C, Coulibaly A, Nikiéma P, Ouédraogo D

59. An analysis of South African patients with rheumatoid arthritis with reference to methotrexate therapy retention
Rashid AGA, Manie M, Moosajee F

CASE REPORTS

70. The Maritime Silk Road: case report of Neuro-Behçet's disease from Somalia with positive HLA-B51 haplotype
Iyer A, Otieno F, Sokhi DS

74. Synovial lipoma arborescens: case report
Basma E, Abujamra AO

77. Severe lupus enteritis, diagnosis and treatment journey: case report
Albalwi FA, Aldegheiman MZ, Albirdisi MR

82. Guidelines to authors

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EDITORIAL BOARD

Glucocorticoid induced osteoporosis – is it relevant in Africa?

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Glucocorticoid Induced Osteoporosis (GIOP) is well recognised as a serious complication of chronic prednisone use for Rheumatic Musculoskeletal Diseases (RMDs). Glucocorticoids (GC) are routinely used in several diverse clinical situations and in varying doses. The mechanisms for bone fragility include increased bone resorption coupled with reduced bone formation. Most reported studies failed to control for important confounding variables such as age, menopause, physical activity, disease activity and treatment of the underlying disease. Studies have been heterogeneous in their selection of patients and controls as well as the method of reporting the bone loss. Some studies have reported on absolute Bone Mineral Density (BMD), and others reported t-scores. The definition of osteoporosis as defined by the World Health Organisation (WHO) may be inappropriate for GIOP; some investigators have recommended a cut-off t-score of -1 rather than -2.5. We were able to identify a few studies on GIOP from Africa. These studies show similar reductions in BMD as in other parts of the globe, affecting both the lumbar spine and hip. There was no information on the treatment of GIOP in the studies from Africa and this is a potential area for future research. Our preliminary findings suggest that a systematic review of the literature may reveal many more publications on GIOP from Africa than is currently appreciated. There is considerable room for further research on GIOP across the African continent, which may contribute to a better understanding of the pathogenesis of this devastating complication of long-term use of GC.

Glucocorticoids (GC) were first used in the treatment of Rheumatoid Arthritis (RA) over 6 decades ago[1]. Their effectiveness was so dramatic that they were subsequently used extensively in the treatment of RA as well as several other Rheumatic Musculoskeletal Diseases (RMDs)[2,3]. Some workers have recommended routine use of these agents in treatment of RA[4-6]. There has been a recommendation that GC would be very useful for RA treatment in Africa, where several synthetic Disease Modifying Anti-Rheumatic Drugs (DMARDs) sDMARDs and bDMARDs (biologic) are not always readily available[7]. The use of glucocorticoids is established in the treatment of RA (usually low-dose), lupus nephritis (usually high-dose) and Polymyalgia Rheumatica (PMR) in intermediate doses. Glucocorticoids are also indicated for the treatment of systemic features of Systemic Lupus Erythematosus (SLE), systemic features of RA, systemic vasculitis, polymyositis and dermatomyositis, to name a few. The overwhelming message from recent reports addresses the adverse effects of these medications, which often make a greater contribution to morbidity and mortality than the underlying diseases[8]. The most concerning long-term side-effect of interest to rheumatologists is the development of Glucocorticoid-Induced Osteoporosis (GIOP) with subsequent bone fragility and fractures.

Bone loss in RMDs is often due to inflammatory mediators such as Tumour Necrosis Factor (TNF), Interleukin 6 (IL6), as well as other osteoclast activators of the TNF class such as RANK-ligand[9-11]. It is possible that these cytokines contribute to localised bone loss described in RA, but their role in trabecular bone loss (bone mineral density (BMD) is often extrapolated from studies of localised osteopaenia. Studies of metacarpal bone density showed that bone loss in RA improves with the use of Disease Modifying Anti-Rheumatic Drugs (DMARDs)[12]. It has also been shown that anti-TNF bDMARD therapy improves BMD in RA subjects over time[9]. Indeed,the bone loss in RA is likely to be multi-factorial and includes the consequences of prolonged uncontrolled inflammation, immobilisation, age, and menopause. GC may reduce inflammation

and limit bone loss due to this mechanism. Overall function and mobility also improve with GC use and may reduce bone loss from other mechanisms, especially in RA. The exact role of GC in studies of GIOP in RMDs is clouded by the inclusion of many of these confounders in the various patient selections. GIOP occurs through several mechanisms, ultimately leading to a synergistic cumulative negative effect of excess bone resorption together with reduced bone formation[13-15]. Some of these postulated mechanisms have been demonstrated in the laboratory[14]. The resorption stimulating pathways are similar to those of post-menopausal osteoporosis[15]. Several studies in RA and SLE have identified a possible relationship between GC use and osteoporosis. However, it is not certain which predictor based on cumulative dose, duration, current dose, ever-user and never-user is the most appropriate method of analysis of data. Some studies used normal controls, while others used matched RA patients not receiving GC[16-20]. The different protocols for the use of GC in the different RMDs also makes comparisons between diseases and across studies difficult.

However, a study comparing metacarpal bone content in RA and SLE against normal controls showed that RA patients suffered greater bone loss than SLE patients, despite larger cumulative doses in the patients with SLE[20,21]. The prevalence of GIOP was extensively reviewed in a global meta-analysis of the published literature[22]. Wang *et al*[23], in a systematic review, reported that there were no studies on GIOP from Africa. In a preliminary search of the literature, we identified at least five publications from Africa on the subject, reported in reputable journals[16-21]. The studies from Africa show similar results[16-21]. The weakness of many of these studies was the inclusion of the confounders mentioned earlier, making it difficult to evaluate the true effects of inflammation, immobilisation, age, menopause, and therapy in the genesis of GIOP in RMDs.

We also found inconsistencies in the definition of GIOP across the various studies, globally. Some studies define GIOP based on a T-score of -1, others use the WHO definition of a T-score of -2.5, and yet others based the diagnosis on vertebral and non-vertebral fractures among patients[15,24,25]. Most studies show that the prevalence is higher in post-menopausal females with RMDs, suggesting that oestrogen deficiency may have a promiscuous effect on bone resorption in the presence of GC therapy[12]. There is clearly a need for further research to better define GIOP in order that we can generalise across studies and cohorts on this subject. This will also allow for the development of suitable guidelines for the detection and treatment of GIOP in these diseases. The treatment of GIOP is addressed in several National guidelines[26,27]. These guidelines are meant to be evidence-based, but the recommended routine use of calcium and vitamin D has not been tested in any Randomized Controlled Clinical Trial (RCT). The anti-resorptive agents such as bisphosphonates are still the mainstay of treatment for GIOP[13]. The therapies used for treating Post-Menopausal Osteoporosis (PMOP) have been used successfully to treat GIOP as well. Newer therapies like teriparatide, an analogue of parathormone, have been successfully used in some patients. Denusomab, a monoclonal antibody directed against RANK-ligand, has been shown to be effective in treating GIOP, and its use is based on the evidence that RANK-ligand may be the major cytokine in the pathogenesis of GIOP[18]. Romosozumab is a monoclonal antibody against sclerostin. It has shown benefits in post-menopausal osteoporosis and men. Some data suggest an important role of sclerostin in mediating the effects of glucocorticoids on bone formation. In addition, treatment with an antibody directed against sclerostin prevented bone loss and reduction of strength in a mouse model. These results highlight the potential beneficial effect of romosozumab on GIOP osteoporosis[28-31]. However, it has not yet been studied in patients on chronic steroids. We were unable to identify studies from Africa which evaluated therapies for the treatment of GIOP, and this is an area requiring further research.

In conclusion, contrary to popular belief, research on GIOP has been undertaken on the African continent. The recent formation of the African Society of Bone and Mineral Research (ASoBMR) provides an ideal forum for research into post-menopausal osteoporosis and GIOP across the African continent. Our current literature search was preliminary, but a systematic review/meta-analysis may reveal more studies being done in Africa than is appreciated. Most of the research has focused on RA, but there are reports in patients with SLE as well. Overall, there is a paucity of GIOP research from Africa, emphasizing the need for more studies from this region of the globe. There is a need for prospective research which will address confounding variables, establish a standard definition and reference point for GIOP, evaluate the effects of treatment and ultimately measure the impact of GIOP on vertebral and non-vertebral fractures in patients with RMDs. All these findings will contribute to improving the quality of life of our patients in Africa (and globally) who suffer from these, often debilitating complications of RMDs and their treatment.

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Covid-19 vaccination in rheumatic diseases: an overview

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Abstract

Background: The Covid-19 pandemic began in Wuhan, China in the late 2019 and spread rapidly all over the world. The pandemic brought about medical challenges to patients with rheumatic autoimmune disease. There were concerns on whether the Covid-19 disease would impact negatively on rheumatic autoimmune diseases outcomes and also whether the vaccination could impact the rheumatic diseases negatively. The other concern was whether the drugs used in management of rheumatic autoimmune diseases would negatively impact the Covid-19 vaccination outcomes.
Objective: To review our understanding of the effect of rheumatic autoimmune disease and DMARDs on Covid-19 vaccination outcomes.
Data source: Available publication databases including but not limited to PubMed, Embase, Scorpio were searched for publications related to Covid-19 vaccination in rheumatic autoimmune disease and the articles were reviewed by the author.
Conclusion: Limited data was available on the impact of rheumatic autoimmune disease and DMARD use on Covid-19 vaccination outcomes.

Key words: Covid-19, Autoimmune rheumatic disease, Vaccination, Outcomes, Challenges, Guidelines

Introduction

The Covid-19 pandemic began in Wuhan, China in the late 2019. In view of the pandemic, there is an unmet clinical need for guidelines on vaccination of patients with Autoimmune Inflammatory Diseases (AIIRD)[1]. The definition of AIIRD in this review predominantly includes but not limited to Spondyloarthritis (SpA), Systemic Lupus Erythematosus (SLE), Connective Tissue Diseases (CTD) and systemic vasculitides.

Critical issues to consider

Points to consider concerning vaccination against Covid-19 in AIIRD include:
(i) Whether the risk to contract Covid-19 is increased among AIIRD patients
(ii) Whether Covid-19 disease is severe in AIIRD patients
(iii) Whether Covid-19 is associated with rheumatic and autoimmune manifestations
(iv) Which vaccines against Covid-19 are available?
(v) The possible safety issues of Covid-19 vaccine in AIIRD patients.
(vi) Whether the vaccines available are effective in patients in AIIRD patients.

Covid-19 outcomes in AIIRD

Systematic reviews have reported a mild increase in the prevalence of Covid-19 among patients with AIIRD[2,3]. The data from Global Rheumatology Alliance (GRA) analysed 3,000 patients with AIIRD[4]. It reported an increased risk of hospitalization (46%) and death (9%) among patients with SLE and vasculitides[4]. However, for the whole population of patients with AIIRD, the main risk factors for hospitalization were similar to those already known in the general population including age and cardiovascular disease[4]. Other risk factors in AIIRD included: high disease activity, treatment with glucocorticoids (>10mg/day prednisolone equivalent dose), rituximab use and some immunosuppressants (azathioprine, cyclophosphamide, mycophenolate, cyclosporin) were related to a higher rate of Covid 19 related deaths[5].

Recent meta-analysis on rheumatic manifestations of Covid-19 included 51 articles[6]. Myalgia and fatigue have been reported in 16% and 36% respectively in patients with Covid-19[6]. Case reports of autoimmune cytopenias[7] and Guillain-Barre Syndrome[8] and autoimmune encephalitis[9] have been published.

Covid-19 may include antinuclear antibodies, anti-SSA and anti-phospholipid antibodies in a large proportion of Covid-19 patients[10].

Covid-19 vaccination in AIIRD

There is generally limited information on the adverse effects of Covid-19 vaccine in patients with AIIRD[11]. Most studies excluded patients with AIIRD except phase 3 trial of BNT 162b2 vaccine which included 118 patients with rheumatic diseases[12]. One study reported a low level of flare (4%) of rheumatic diseases about 6 days with a Covid-19 vaccine[13]. Another study reviewed outcomes of 6 vaccines[14]. Available evidence has shown that Covid-19 vaccination among patients with Spondyloarthritis (SpA) among other AIIRD to be effective, and safe even with DMARD use[15].

Various recommendations and guidelines have been developed by professional organisations regarding management of AIIRD during the Covid-19 pandemic. These include European Alliance of Association for Rheumatology (EULAR)[16], American College of Rheumatology (ACR)[17] and National Psoriasis Foundation[18]. Treatment with TNF inhibitors does not pose a general risk to humoral responses in most SpA patients but their use in patients with IBD associated arthritis may alter immune responses to vaccines[19]. Limited evidence suggests that use of MTX and JAK inhibitors in patients with AIIRD may interfere with vaccine responses hence the recommended treatment modification advised by ACR[17]. Prednisolone >10mg equivalent dose[20], MTX[21], and mycophenolate[22] were associated with decreased humoral responses. Rituximab was associated with significantly reduced humoral responses[21]. IL-6 receptor inhibitors were associated with unimpaired humoral responses[23], while abatacept showed inconsistent data[24]. Having discussed all the above, it is important to note that physician recommendation was the main factor in vaccine acceptance[25].

Despite the challenges of DMARDs in Covid-19 vaccination, the interleukin-6 inhibitor, tocilizumab has been shown to reduce need for mechanical ventilation and mortality in patients with severe Covid-19 disease[26]. Finally, the African League Against Rheumatism (AFLAR) have developed guidelines for the management of rheumatic diseases during the Covid-19 pandemic[27] which rheumatologists working in Africa would be advised to understand and follow.

Conflict of interest: The author declares no conflict of interest.

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Research article

Prevalence of neuropathic pain in patients with common low back pain with radiculalgia in sub Saharan Africa: a bicentric cross-sectional study of about 409 patients

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Abstract

Background: Neuropathic Pain (NP) is defined as pain caused by injury or disease of the somatosensory nervous system.
Objective: To study the frequency of neuropathic pain among patients with common low back pain with radiculalgia in sub-Saharan Africa.
Methods: This was a bicentric cross-sectional study carried from February 2015 to 30th July 2015 in the first center and from February 2017 to 30th July 2017 in the second center. The study lasted six months in each study site. All patients with a common low back pain with radiculalgia were included. Those without radiculalgia and those without the common character, were not included. The common character was based on the absence of biological inflammation (normal haemogram and sedimentation rate, negative C-Reactive-Protein). DN4 questionnaire was used for the diagnosis of neuropathic pain.
Results: Four hundred and nine patients with common low back pain with radiculalgia were included. There were 278 females (67; 97%) and 131 males (32; 03%), for a sex ratio of 0.47. The average age was 51.75 ± 13.84 years with extremes of 16 and 88 years. One hundred and seventy-five patients (42.8%) had NP. Statistical analysis showed a statistically significant association between NP and age over 60 years and clinical radicular syndrome.
Conclusions: Our study found a high frequency of neuropathic pain during common low back pain with radiculalgia in sub-Saharan Africa patients. Age over 60 years and poorly systematized radiculalgia were associated to NP.

Key words: Neuropathic pain, Low back pain, DN4, Africa

Introduction

Neuropathic Pain (NP) is defined as pain caused by injury or disease of the somatosensory nervous system[1]. Many diagnostic tools have been developed, one of the most widely used for clinical and epidemiological studies is the DN4 questionnaire (Neuropathic pain in 4 questions)[2]. The overall prevalence of chronic pain with neuropathic features is between 7% and 10%[3,4]. In UK, the prevalence of chronic NP is between 8.2% and 8.9% among two population studies[5]. In sub-Saharan Africa, a population-based study in Benin reported a 6.3% prevalence of NP[6]. Low Back Pain (LBP) is a cause of NP and the presence of radiculalgia appears to be statistically associated with NP[7,8]. Many studies on NP in general and particularly during low back pain with radiculalgia have been performed worldwide[3,4,7-10]. In sub-Saharan Africa, we found two studies, carried out respectively by Ouédraogo *et al*[11] in Ouagadougou (Burkina Faso) and Doualla *et al*[12] in Douala (Cameroon) that evaluated the frequency of neuropathic pain during LBP and low back pain with radiculalgia; they reported frequencies of 49.5% and 28.1% respectively. In order to minimize the biases related to the environment of the series, we conducted a new study in hospitals in Burkina Faso and Ivory Coast. The objective of this bicentric study was to evaluate the frequency of NP during common low back pain with radiculalgia.

Materials and methods

A bicentric cross-sectional study was performed from February 2015 to 30th July 2015 in Abidjan (Ivory Coast) and from February 2017 to 30th July 2017 in Ouagadougou (Burkina Faso. The rheumatology wards of the Cocody Teaching Hospital in Abidjan (26 beds) and the Bogodogo Teaching Hospital in Ouagadougou (33 beds) were the study frameworks. The study population consisted of consecutive patients presenting with common low back pain and radiculalgia during the study period. Full blood count ESR CRP and lumbar spine X-rays were performed in all patients.

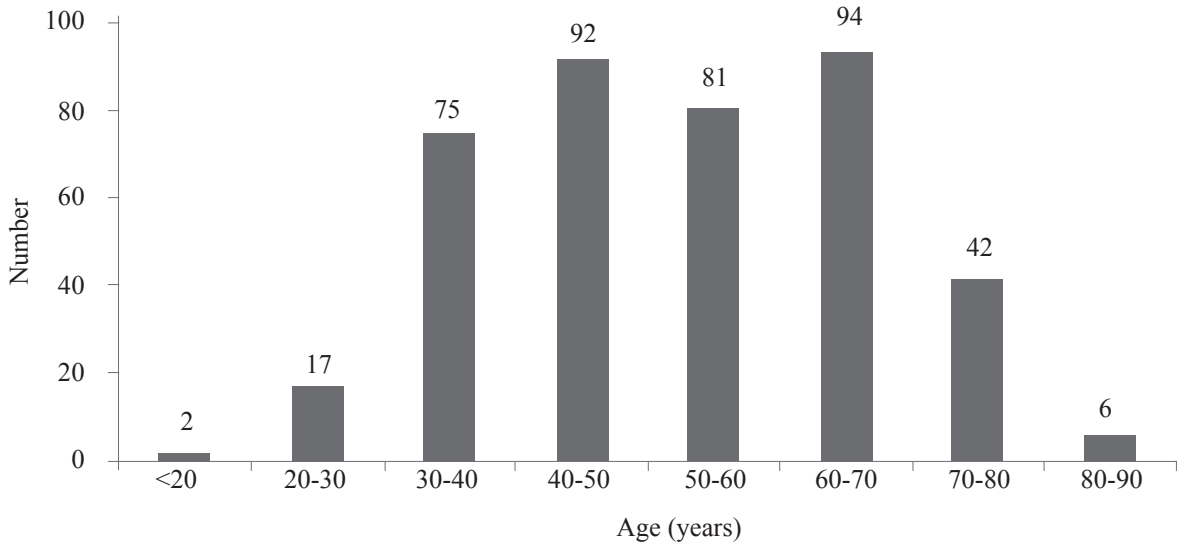
Lumbar CT and MRI were not routinely performed. Patients presenting with low back pain and pelvic, crural or sciatic irradiation were included in our study. The diagnosis of Neuropathic Pain (NP) was made in patients with at least four items on the DN4 questionnaire[2]. LBP or LBP with radiculalgia associated with a traumatic, infectious, rheumatic or tumour aetiology was excluded. Pain intensity was assessed on a Visual Analogue Scale (VAS) rated at 10. Data were collected through questions asked by a rheumatologist to the patient, alone or with the assistance of a companion who provided translation if necessary. A physical examination was also performed by the same rheumatologist. In addition to the DN4 items, the questionnaire included socio-demographic data (age, gender, occupation, weight, height and Body Mass Index (BMI)), clinical data (history of low back pain, duration of current episode, circumstances of onset, pain intensity, type of low back pain, type of radiculalgia, spinal and root examination data), and para-clinical data. Patients were informed and freely consented to take part in the study. The results were analyzed using the Epi info 3.5.1 software. The Chi-square test was used to perform comparisons of variables. Any probability value (p) less than 0.05 was considered statistically significant.

Results

Characteristics of the study population

Four hundred and nine patients with common low back with radicular pain were included. There were 278 females (67.97%) and 131 males (32.03%), for a sex ratio of 0.47. The average age was 51.75 ± 13.84 years with extreme ages 16 and 88 years. Two frequency peaks were observed between 40 and 50 years and then between 60 and 70 years. Figure 1 shows the distribution of patients by age group. According to occupation, housewives, traders and office workers were most represented, respectively 120 (29.34%), 110 (26.90%) and 76 (18.60%). The average BMI was 26.86 ± 4.83 kg/m^2 with extremes of 17.15 and 44.14 kg/m^2. Two hundred and forty-four patients (61.6%) were overweight (BMI ≥ 25 kg/m^2).The lumbar history, mode of symptom onset, age of onset and type of radiculalgia were summarized in Table 1. Spinal stiffness was observed in 396 patients (96.8%) and clinical radicular syndrome in 249 patients (60.9%). CT and MRI scans were performed on 132 (32.3%) and 11 (2.7%) patients respectively (Table 2).

Figure 1: Distribution of patients by age



Frequency and factors associated with neuropathic pain

One hundred and seventy-five patients had NP, a frequency of 42.8%. The mean number of DN4 items per patient was 4.23 ± 0.4 with extremes of 4 and 6 items (Table 3). Statistical analysis showed a statistically significant association between NP and age over 60 years and between NP and clinical radicular syndrome. The association between NP and patient's socio-demographic and clinical variables is summarized in Table 4. Facet joint osteoarthritis and disc protrusion were statistically associated with NP as shown in Table 5.

Table 1: Patient history and functional signs

	Features	No.	(%)
Background (n=409)	Chronic low back pain	312	76.3
	No previous history	87	21.3
	Spinal anaesthesia	5	1.2
	Lumbar surgery	3	0.7
	Lumbar trauma	2	0.5
Start mode (n=344)	Progressive	289	84
	Brutal	55	16
Age of pain (n=409)	Acute	39	9.53
	Sub-acute	62	15.16
	Chronic	308	75.31
Type of radiculalgia (n=409)	L5 nerve root sciatica	122	29.83
	Poorly systematized sciatica	120	29.34
	S1 nerve root sciatica	104	25.43
	Poorly systematized cruralalgia	40	9.78
	L4 Cruralgia	23	5,62
Intensity of pain (VAS) (n=361)	7-10	294	81,5
	4-6	64	17,7
	1-3	03	0,8

Table 2: Frequency of radiological lesions in patients*

	No.	(%)
Discarthrosis	355	86.8
Lumbar osteoarthritis	287	70.2
Facet Joint Osteoarthritis (FJOA)	132	32.3
Disc protrusion	59	14.4
Herniated disc	46	11.2
Spondylolisthesis by FJOA	44	10.8
Scoliosis	38	9.3
Hyperlordosis	35	8.6
Isthmic lysis without listhesis	21	5.1
Spondylolisthesis by isthmic lysis	16	3.9
Lumbarization of the 1st sacral vertebra	10	2.4
Osteoporotic vertebral collapse	6	1.5
Transverse mega-apophysis of L5	05	1.2
Sacralization of 5th lumbar vertebra	02	0.5

*a patient could have multiple radiographic lesions

Table 3: Frequency of DN4 patient items*

	No.	(%)
Burn	316	77.3
Tingling	214	52.3
Electric shocks	129	31.5
Numbness	125	30.6
Picks	124	30.3
Itching	85	20.8
Hypoesthesia with tact	62	15.2
Hypoesthesia with stinging	46	11.2
Painful cold	35	8.6
Painful rubbing	24	5.9

*a patient could have had several items.

Table 4: Socio-demographic, clinical factors and neuropathic pain.

	NP+		NP-		
	No.	(%)	No.	(%)	P
Female gender	124	44.6	154	55.4	0.14
Age > 60 years old	64	51.6	60	48.4	0.00
Housewife	53	44.2	67	55.8	0.34
Overweight	109	44.7	135	55.3	0.18
History of chronic low back pain	132	42.9	176	57.1	0.48
Sciatica	154	44.5	192	55.5	0.05
Severe pain	135	45.9	159	54.1	0.05
Lumbar stiffness	174	43.9	222	56.1	0.00
Poorly systematized radiculalgia	127	51	122	49	0.00

NP+ = Presence of neuropathic pain ; NP- = no neuropathic pain ; No. = number

Table 5: Radiological lesions and neuropathic pain

	NP+		NP-		
	No.	(%)	No.	(%)	P
Discarthrosis	156	43.9	199	56.1	0.11
Lumbar osteoarthritis	138	48.1	149	51.9	0.00
Facet Joint Osteoarthritis (FJOa)	72	54.5	60	45.5	0.00
Disc protrusion	34	57.6	25	42.4	0.00
Herniated disc	24	52.2	22	47.8	0.08
Spondylolisthesis by FJOa	24	54.5	20	45.5	0.05
Scoliosis	19	50	19	50	0.17
Lumbar hyperlordosis	16	45.7	19	54.3	0.35
Isthmic lysis	07	33.3	14	66.7	0.19
Lumbarization of 1st sacral vertebra	06	60	04	40	0.14
Spondylolisthesis by isthmic lysis	05	31.3	11	68.7	0.17
Osteoporotic compaction	04	667	02	33.3	0.13
Transverse mega-apophysis of 5th lumbar vertebra	03	60	02	40	0.23

NP+: Presence of neuropathic pain; NP- = no neuropathic pain; No. = number

Discussion

Frequency of NP was 42.8% in patients with common low back with radicular pain. Age over 60 years, spinal stiffness and radiculopathy were statistically associated with NP. In terms of imaging, lumbar osteoarthritis, disc protrusion and facet joint osteoarthritis were also significantly associated with neuropathic pain.

Any interpretation of these results must take into account the limitations and biases of our study. As CT and MRI scans were not performed in all patients, other types of disc or degenerative lesions (herniated disc, disc protrusion, facet joint osteoarthritis) or inflammatory lesions (spondylodiscitis) may have been overlooked in our study. Absence of biological inflammatory syndrome in CRP and sedimentation rate might have minimized these cases.

The average age of the patients was 51.75 ± 13.84 years. This is comparable to the data in the literature[12-14]. Our series were dominated by housewives and shopkeepers. Although low back pain affects 70% of the working-age population, the predominance of housewives and shopkeepers may be due to a selection bias with regard to the proportion of this socio-professional category in African populations[15]. The household activities of housewives and the predominantly informal nature of trade in our context could also explain these results.

NP frequency was 42.8%. This frequency is higher than the 28.1% reported by Douala *et al*[12] in Cameroon. However, it is comparable to the results previously reported in Burkina Faso by Bouhassira *et al*[9] and Kaki *et al*[13] in Saudi Arabia, which were 49.5% and 54.7% respectively. According to two meta-analyses published in 2017, NP frequency varies between 19% and 80% during LBP and LBP with radiculalgia[4,7]. This significant variation in the frequency of NP in common LBP and LBP with radiculalgia could be explained by the diversity of study methods, the heterogeneity of the study populations, and especially the multitude of languages in which the DN4 questionnaire is translated and administered.

Age over 60 years seems to predispose to the presence of NP during common low back pain with radiculalgia ($p < 0.01$). Adoukonou *et al*[6] also reported that elderliness was associated with neuropathic pain. In our series, the history of chronic low back pain was not statistically associated with NP ($p = 0.48$). Some studies have shown that both acute and chronic low back pain are not associated with NP[4,7]. Radiculopathy was statistically associated with NP ($p<0.01$). This could be explained by the fact that radiculopathy is the expression of nerve root pain. Facet joint osteoarthritis and disc protrusion were statistically associated with NP ($p < 0.01$). In low back pain with radiculalgia, functional alterations of the nerve roots may result from compression due to significant spinal canal stenosis[16]. Ductal narrowing by disc protrusion, intraspinal osteophytes, and hypertrophy of ligamentum flavum frequently associated with facet joint osteoarthritis could explain this association. Our study did not find a significant association between disc herniation and NP ($p = 0.08$). Symptomatic disc herniation is generally associated with a biochemical inflammatory phenomenon and therefore rather responsible for pain due to excess nociception; also, the natural evolution of a disc herniation is the improvement of clinical symptoms but also a decrease in volume, or even disappearance of the hernia in more than half of the cases[16]. Only 20% to 40% of radiological disc herniations are symptomatic according to the literature[16,17]. The excess weight found in our study (61.6%) and frequently associated with low back pain and low back pain with radicular pain does not seem to be statistically related to the occurrence of NP.

Conclusions

This study found a high frequency of NP in common LBP with radicular pain. Burning sensation, electric shocks and tingling were the most common neuropathic features found. A statistically significant association was found between NP and age over 60 years, physical radicular syndrome, facet joints osteoarthritis and disc protrusion. The wide variety of languages spoken by patients and the difficulties in translating the DN4 questionnaire into these languages may have influenced our results. A validation study of the DN4 questionnaire in our national languages may allow a more accurate assessment of NP in the context of low back pain with radicular pain.

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An analysis of South African patients with rheumatoid arthritis with reference to methotrexate therapy retention

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Abstract

Background: Methotrexate (MTX) is a Disease-Modifying Antirheumatic Drug (DMARD) for treating various types of inflammatory arthritis, including Rheumatoid Arthritis (RA).
Objective: This article evaluates MTX retention rates and reasons for discontinuation in patients with RA in South Africa. The article also seeks to establish and draw attention to factors that may affect retention.
Method: The study population comprised of 230 patients with RA treated with MTX attending the Rheumatology Department of the Tygerberg Academic Hospital.
Results: Seventy nine patients (34.3%) terminated MTX and 151 patients continued giving a retention rate of 65.7%. The reasons for MTX termination were persistent high disease activity and presumed ineffectiveness (30.4%), nausea and vomiting (25.3%), non-compliance (11.4%), lung toxicity (8.9%), pregnancy-related (7.6%), and hepatotoxicity (5.1%). Clinical factors were not significant predictors of MTX adherence and MTX retention increased with age. Patients aged 65 years and older were twice as likely to have multiple comorbidities and were more likely to continue with treatment.
Conclusions: The duration of MTX treatment correlated with increased age. High retention rate of MTX is encouraging, as it remains the anchor drug among DMARDs in the treatment of RA. Further large scale, prospective, multicenter studies are needed to clearly understand MTX retention rates in patients with RA.

Key words: Methotrexate, Therapy, Retention, Rheumatoid Arthritis, Patients, South Africa

Introduction

Rheumatoid Arthritis (RA) is a chronic multiorgan autoimmune inflammatory disease. If untreated, RA results in poor clinical outcomes, including severe progressive structural joint damage, functional disabilities, and increased morbidity and mortality[1]. To avoid joint damage, inflammation in patients with RA should be suppressed as much as possible. The main goal of treating RA in patients is to improve their quality of life by reducing the symptoms and clinical disease[2]. This will lead to improving the functional outcome of patients with RA in the long term.

Methotrexate (MTX) is the most frequently used Disease-Modifying Antirheumatic Drug (DMARD) and remains an anchor therapy despite the advent of biological agents for treating RA. The combination of effectiveness and a commendable safety record, when compared to other DMARDs, renders MTX as the first-line treatment for most patients with RA[3]. MTX is extensively used for other autoimmune conditions such as psoriasis, uveitis, and inflammatory bowel diseases. Despite these advantages, there are limited reports on MTX retention rates.

To counter potential toxicity, steps are taken to ensure the safe use of MTX. Hepatotoxicity, gastrointestinal side effects (including nausea and diarrhoea), leukopenia and lung toxicity are well-documented side effects[4]. Considering hepatotoxicity, there are recommendations that patients have liver function tests performed before the commencement of MTX therapy, at least three times a year while receiving the therapy[5]. Some centers also perform routine Hepatitis B surface antigen (HBsAg) and Human Immunodeficiency Virus (HIV) screening. Prior to initiating MTX therapy, a history of liver disease or the use of hepatotoxic drugs, including alcohol should be addressed. This history is relevant as these agents may potentiate liver toxicity, in the setting of MTX use[3]. Folic acid is also used when a patient is on MTX. Folic acid protects the healthy cells in a patient's body by reducing the side effects of MTX; it makes a patient less likely to be vomiting or have diarrhoea[6].

Older patients and those with renal impairment should be monitored

more closely for the development of leucopenia[7]. Considering MTX being an immunosuppressive drug, chest radiographs are performed to exclude Pulmonary Tuberculosis (PTB) or co-existing lung disease[8]. Also, MTX being teratogenic, child-bearing females are routinely advised to use effective contraception or avoid its use if a pregnancy is planned. Patients are also informed of MTX's potential to temporarily reduce fertility in males[8].

Agarwal, *et al*[9] undertook a cross-sectional study to evaluate the retention rates of DMARDs in patients with RA. The study included 102 patients, and a total of 375 total DMARD courses were administered to these patients. The average retention time for MTX was found to be 28 months. This was slightly longer compared with the other DMARDs. The most common reason for DMARDs discontinuation was ineffectiveness (51.1%), followed by Adverse Events (AE) (24.3%) and the disease being considered under control (16.3%). The rest of the discontinuations were due to various reasons such as planned pregnancy (2.2%), concomitant comorbidities (2.2%), non-compliance (1.3%), financial reasons (1.1%), preference for alternative medical therapy (1.1%), and planned surgery (0.4%)[9].

A Norwegian study by Lie *et al.*[10] compared the efficacy and retention rates of MTX administered to patients with Psoriatic Arthritis (PsA) and RA. It was found that the 2-year retention rates of MTX treatment for PsA and RA were 65% and 66%, respectively. However, the reasons for treatment termination were similar among the two groups. It was also determined that after 6 months, there was an improvement in assessed disease activity and the patients' quality of life. This study also found out that Adverse Events (AEs) were the main reason for drug termination, followed by lack of efficacy, and that nausea was the most frequently reported AE, including elevated liver enzymes. A slightly higher proportion of patients with PsA (4.7%) than those with RA (3.3%) discontinued MTX because of elevated liver enzymes[10,11]. GIT toxicity related to methotrexate was the most common AE causing drug discontinuation in both groups.

Based on our understanding, no literature was published to address the question on MTX retention rates in South Africa. This study aimed to assess the rate of MTX retention and causes of MTX termination in South African patients with RA at Tygerberg Academic Hospital.

Materials and methods

This was a retrospective cross-sectional study conducted in the Tygerberg Academic Hospital's Division of Rheumatology. We identified 230 RA patients who had been administered MTX as a DMARD, over a six-month period. The study population included RA patients dating back to January 2009. The patients were between the ages of 19 and 90 years, and categorized into three age domains : namely young patients with RA (YRA; ≤ 40 years), middle-aged patients with RA (MRA; 41-65 years), and older patients with RA (ORA; > 65 years). Each enrolled patient was allocated a number under where their data were recorded to ensure anonymity. The details recorded for each participant were name (only on the confidential list linked to the allocated number), folder number, demographics (e.g., age, sex, and race), duration of disease, treatment, complications, and MTX dosage before treatment termination. Additionally, any adverse effects associated with MTX were recorded, and disease activity was monitored using the Clinical Disease Activity Index (CDAI)[12].

Historical information on basic laboratory test monitoring with full blood count tests and the participants' previous results of renal and liver function tests were collected. Screenings for recorded data relating to more specific tests, such as the serological method to determine the Rheumatoid Factor (RF), anti-Cyclic Citrullinated Peptide (anti-CCP test), and patients' HIV and viral hepatitis status were also performed.

The reasons for MTX termination were classified as AEs, ineffectiveness, non-compliance, and pregnancy related. An AE is any side effect, such as nausea and vomiting that resulted in the discontinuation of treatment. In effectiveness was defined as ongoing active disease despite MTX therapy as measured by the CDAI, and requiring a change in the drug regimen. Non-compliance refers to patients not taking their prescribed medication correctly. The three age groups (YRA, MRA, and ORA) are shown in Table 1.

Statistical analysis

Descriptive (summarized) statistics were used to explore our data. We report the measurement of the variability of the numerical variables as "mean" ± Standard Deviation (SD) for the variables following a normal distribution and as median [confidence interval] for the numerical variables that did not follow a normal distribution. The categorical variables were reported as "counts" (% Frequency).

To investigate potential differences of the variables between the "Age groups", and treatment continuity, a Fisher's Exact Test[13] for the categorical variables were conducted. Two survival analyses (Kaplan Meier and Cox Proportionate Hazards regression) were conducted, one for the "Days to treatment" and the other for the "Days to MTX termination", for the two groups of age "Age on diagnosis groups" and "Age groups".

For the survival analyses, the Kaplan-Meier[14] was used to estimate the survival probability each time an event occurs as well as compute survival curves. The statistical method was also used to investigate the null hypothesis of no difference in survival between two or more independent groups the Log Rank test was utilized. Finally, Cox proportional[15] regression models for each of the survival analyses were applied.

Results

Baseline characteristics and measures of associations

Gender: Across all age groups females dominated aged below 40 years (95.6%), 41-65 years (77.4%) and above 65 years (79.2%).

Table 1: Descriptive statistics of the participants stratified by the "Age groups"

Variables	Age groups			
	40 years and younger (N = 23)	41- 65 years (N = 159)	65+ years (N = 48)	P-value sig.
Gender				0.14
Female	22 (95.6%)	123 (77.4%)	38 (79.2%)	
Male	1 (4.3%)	36 (22.6%)	10 (20.8%)	
Ageat time of survey	33.3 ± 5.0	55.2 ± 6.2	72.9 ± 5.6	*< 0.01
Age at diagnosis	27.0% [23.5;30.5]	47.0% [40.0;54.0]	63.0% [56.0;66.5]	**< 0.01
Duration of treatment	248.0 [120.5;1355.0]	248.0 [11.0;620.5]	283.5 [113.0;887.5]	0.44
Starting †MTX dose (mg/W)				0.42
10/W	0 (0.0%)	3 (1.9%)	3 (6.3%)	
12.5/W	2 (8.7%)	23 (14.5%)	11 (22.9%)	
15/W	14 (60.9%)	88 (55.3%)	20 (41.7%)	
20/W	5 (21.7%)	27 (16.9%)	6 (12.5%)	
22.5/W	0 (0.0%)	0 (0.0%)	1 (2.1%)	
25/W	0 (0.0%)	1 (0.629%)	0 (0.0%)	
30/W	0 (0.0%)	1 (0.629%)	0 (0.0%)	
7.5/W	2 (8.7%)	16 (10.1%)	7 (14.6%)	
Other ‡DMARDS				0.39
§AZA	0 (0.0%)	2 (1.3%)	0 (0.0%)	
¶LEF	1 (4.3%)	9 (5.7%)	3 (6.3%)	
††MMF	1 (4.3%)	2 (1.3%)	0 (0.0%)	
None	15 (65.2%)	86 (54.1%)	34 (70.8%)	
Rituximab	1 (4.3%)	0 (0.0%)	0 (0.0%)	
‡‡SSZ	5 (21.7%)	51 (32.1%)	10 (20.8%)	
SSZ, LEF	0 (0.0%)	8 (5.0%)	1(2.1%)	
Treatment stopped	0.98			
No	15 (65.2%)	103 (64.8%)	30 (62.5%)	
Yes	8 (34.8%)	56 (35.2%)	18 (37.5%)	
Disease activity before MTX termination	18.7 ± 5.8	18.0 ± 9.9	18.7 ± 25.4	0.99
Disease activity after MTX termination	8.0 [5.0;11.5]	12.0 [6.5;15.0]	9.0 [6.5;11.5]	0.73
Comorbidity				***< 0.01
Multiple comorbidities	2 (8.7%)	53 (33.3%)	34 (70.8%)	
None	17 (73.9%)	61 (38.4%)	7 (14.6%)	
Single comorbidity	4 (17.4%)	45 (28.3%)	7 (14.6%)	
Complications of disease				0.09
Carpel Tunnel Syndrome	0 (0.0%)	0 (0.0%)	1 (2.1%)	
§§GERD	0 (0.0%)	3 (1.9%)	4 (8.3%)	
Multiple bone deformity	0 (0.0%)	1 (0.6%)	0 (0.0%)	
Necrotizing autoimmune myopathy	0 (0.0%)	1 (0.6%)	0 (0.0%)	
Nodular rheumatoid disease	0 (0.0%)	2 (1.3%)	0 (0.0%)	

Variables	Age groups			P-value
	40 years and younger (N = 23)	41- 65 years (N = 159)	65+ years (N = 48)	sig.
None	23 (100.0%)	145 (91.2%)	36 (75.0%)	
Osteoporosis	0 (0.0%)	3 (1.9%)	5 (10.4%)	
Panniculitis, Ruptured Baker Cyst	0 (0.0%)	1 (0.6%)	0 (0.0%)	
¶¶RA – †††ILD	0 (0.0%)	3 (1.9%)	2 (4.2%)	
Rheumatic disease				0.49
Giant Cell Arteritis/RA overlap syndrome	0 (0.0%)	1 (11.1%)	0 (0.0%)	
‡‡‡JIA/RA overlap syndrome	3 (75.0%)	1 (11.1%)	0 (0.0%)	
Psoriasis/RA overlap syndrome	0 (0.0%)	1 (11.1%)	0 (0.0%)	
Scleroderma/RA overlap syndrome	0 (0.0%)	1 (11.1%)	0 (0.0%)	
Seronegative RA	0 (0.0%)	2 (22.2%)	0 (0.0%)	
§§§ SLE / RA overlap syndrome	1 (25.0%)	1 (11.1%)	0 (0.0%)	

Note: Numerical variables that follow a normal distribution are expressed as mean ± standard deviation, and the numerical variables that do not follow a normal distribution are expressed as median [Confidence Interval]; the categorical variables are expressed as counts (%). The significant results ($p < 0.05$) are indicated as *p-value for Age, **p-value for Age at diagnosis, and ***p-value for Comorbidity. †Methotrexate; ‡Disease-modifying antirheumatic drugs;§Azathioprine; ¶Leflunomide; ††Mycophenolic acid;‡‡Sulfasalazine;§§Home conditions;¶¶Rheumatoid arthritis; †††Interstitial lung disease; ‡‡‡Juvenile idiopathic arthritis; §§§Systemic lupus erythematosus

Age at time of survey: Twenty-two participants were within the age of 28.3 and 38.3 years, 159 participants were within 49.0 and 61.4 years, and 48 participants were within 67.3 and 78.5 years.

Age at diagnosis: Sixty-three per cent were >65 years of age, 47% were 41-65 years, and those aged below 40 years (27%).

The retention rates of MTX: Retention rates were similar among different age groups (65.2% (young people) vs 64.8% (41-65 years) vs 62.5% (65+ years). Those who discontinued treatment also did not differ in terms of age groups.

Comorbidities: Participants who had multiple comorbidities were twice as likely to be aged above 65 years (70.8%), compared to those aged 41-65 years (33%), and those aged below 40 years (8.7%). Those with single comorbidities were more likely to be aged 41-65 years (28.3%), compared to other age groups. Those who had no comorbidities were more likely to be younger than 40 years of age.

Complications of disease: Only 10% of patients experienced complications of their disease ($p<0.1$). The older age group (65+ years) have experienced more complications (75%) compared to those aged 41-65 years (91.2%) or those aged less than 40 years (100%). Carpel Tunnel Syndrome, GERD (Gastroesophageal Reflux Disease), osteoporosis, Ruptured Baker Cyst, multiple bone deformity, and most other complications did not occur among those aged less than 40 years.

Non-significant factors

Starting MTX dosage: The most common MTX starting dose was 15mg per week. Although 12.5mg was more common in older patients. A starting dose on >20mg/ week of MTX was rarely used.

Disease activity before MTX termination: The results suggest that there were no differences between the three age groups, YRA (18.6%) and those aged 41-65 years (18.7%) or those aged 65+ years (18.7%) in terms of disease activity before MTX termination.

Disease activity after MTX termination: The results suggest that there were no differences between the YRA (8%) and those aged 41-65 years (12%), or those aged 65+ years (9%) in terms of disease activity after MTX termination.

Other DMARDs: The results show that other DMARDS used in combination with MTX were not predominant in this sample. MTX monotherapy was more likely among the aged 65+ years (70%) as compared to the other two groups (54% and 65.2%, respectively). The combination of DMARDs, namely: MTX, SSZ & LEF and MTX and LEF were more likely to be used in the MRA (41-65 years) age group. Rituximab was used in one patient only aged below 40 years.

Rheumatic disease association: The association with other rheumatic diseases were observed more among those aged less than 40 years (75%), followed by those aged 41-65 years (11.1%) and none among patients aged

Table 2: Tabularized illustration of treatment stopped

Variables	Treatment stopped		P-value sig.
	No	Yes	
	(N = 148)	(N = 82)	
Gender			0.497
Female	119 (80.95%)	63 (76.83%)	
Male	28 (19.05%)	19 (23.17%)	
Age	56.58 ± 11.83	56.84 ± 12.62	0.876
Age at diagnosis	48.45 ± 12.44	45.59 ± 12.95	0.101
Duration of treatment (Days to treatment)	249.50 [55.00;603.00]	258.00 [11.00;620.50]	0.995
Starting †MTX dose (mg/W)			0.592
10/W	4 (2.70%)	2 (2.44%)	
12.5/W	20 (13.51%)	16 (19.51%)	
15/W	79 (53.38%)	43 (52.44%)	
20/W	28 (18.92%)	10 (12.20%)	
22.5/W	1 (0.68%)	0 (0.0%)	
25/W	1 (0.68%)	0 (0.0%)	
30/W	0 (0.0%)	1 (1.22%)	
7.5/W	15 (10.14%)	10 (12.20%)	
Comorbidity			0.501
Multiple comorbidities	53 (35.81%)	36 (43.90%)	
None	57 (38.51%)	28 (34.15%)	
Single comorbidity	38 (25.68%)	18 (21.95%)	
Other ‡DMARDS			*0
§AZA	1 (0.68%)	1 (1.22%)	
¶LEF	1 (0.68%)	12 (14.63%)	
††MMF	2 (1.35%)	1 (1.22%)	
None	107 (72.30%)	28 (34.15%)	
Rituximab	1 (0.68%)	0 (0.0%)	
‡‡SSZ	35 (23.65%)	31 (37.80%)	
SSZ, LEF	1 (0.68%)	8 (9.76%)	
SSZ, MMF	0 (0.0%)	1 (1.22%)	
Complications of disease			0.073
Carpel Tunnel Syndrome	1 (0.68%)	0 (0.0%)	
§§GERD	7 (4.73%)	0 (0.0%)	
Multiple bone deformity	0 (0.0%)	1 (1.22%)	
Necrotizing autoimmune myopathy	0 (0.0%)	1 (1.22%)	
Nodular rheumatoid disease	1 (0.68%)	1 (1.22%)	
None	131 (88.51%)	73 (89.02%)	
Osteoporosis	6 (4.05%)	2 (2.44%)	
Panniculitis, Ruptured Baker's Cyst	0 (0.0%)	1 (1.22%)	
¶¶RA – †††ILD	2 (1.35%)	3 (3.66%)	

The significant results ($p < 0.05$) are indicated as *p-value for DMARDS, †Methotrexate; ‡Disease-modifying antirheumatic drug;§Azathioprine; ¶Leflunomide; ††Mycophenolic acid; ‡‡Sulfasalazine; §§Home conditions; ¶¶Rheumatoid arthritis; †††Interstitial lung disease

65+ years. Seronegative RA was observed only among those in the MRA (41-65 years) age group and JIA in the YRA (<40 years) age group only.

Measures of associations between correlates of MTX and duration of treatment

When the treatment stoppage/continuation is the dependent variable, observation shows that other DMARDS and complications of disease were associated with treatment continuity as illustrated in Table 2.

Significant factors

Exposure to DMARDS: The majority of patients were prescribed MTX monotherapy and a third (34.2%) combination DMARD therapy. Out of the 95 patients who were prescribed other DMARDS, 67 received SSZ and 22 received LEF as add on therapy. MTX & SSZ, MTX & LEF, and the combination of MTX/SSZ & LEF were the three most prevalent DMARD combinations in this study.

The complications of disease: Ten percent of patients experienced complications of their disease ($p<0.1$), 6/8 patients with osteoporosis (75%) all seven with GERD complications and other complications all patients with multiple bone deformities, necrotizing autoimmune myopathy, panniculitis or Ruptured Baker's Cysts were more likely to continue with treatment. There were no differences in terms of retention rates of MTX among patients with RA related-ILD, and those with rheumatoid nodules.

Comorbidities: The results show that there were no differences overall between patients who had comorbidities and those without, for retention of MTX treatment. Patients with multiple comorbidities however were more likely to discontinue treatment (43.9% vs 35.8%), compared with those with a single comorbidity (25.7% vs 22%).

Starting MTX dose(mg/week): Results indicate that overall the initial MTX dose was not associated with treatment continuation or stoppage.

Table 3: Tabularized illustration of causes of termination

Variables	N	Descriptive statistics	Class
Cause of termination	79		Categorical
†GIT toxicity, nausea and vomiting		20 (25.32%)	
High disease activity - ineffectiveness		24 (30.38%)	
Hepatotoxicity		4 (5.06%)	
Lung toxicity		7 (8.86%)	
‡MTX induced leucopoenia		4 (5.06%)	
Non-compliance		9 (11.39%)	
Pregnancy-related		6 (7.59%)	
§PTB		3 (3.80%)	
Renal toxicity		1 (1.27%)	
Skin infection		1 (1.27%)	

Demographic factors: Neither gender or age were associated with retention in MTX; the same applies to days to treatment/duration of treatment, those whose mean days of duration was higher, were more likely to continue with treatment (258 days vs 249 days). Results suggest that the longer the duration of treatment, the more likely the patient would be to continue with MTX treatment.

Reasons for termination

Seventy-nine (34%) of the 230 patients stopped and 151 (66%) continued taking MTX. High disease activity (ineffectiveness) (30.4%) and GIT toxicity (nausea and vomiting) (25.3%) were the main reasons for termination and other causes are listed in the Table 3.

Survival analysis

The study sought to investigate factors that were predictors of MTX treatment duration and termination. MTX termination was classified as AEs, ineffectiveness, non-compliance, and pregnancy related. The following two models provide the results in Tables 4 and 5, respectively. For 'days to treatment', age on diagnosis group (60, 80) were 2.2 times more likely to associate with days to treatment ($\beta=2.2$, $p<0.05$), compared to the younger age groups, while the age group (20,40) demonstrated the lowest times to be associated with days to treatment ($\beta=0.7$, $p<0.05$). The older the age group, the more the number of days to treatment shown in Table 4. For 'days to MTX termination', age on diagnosis group (60,80) were nine times more likely to experience fewer days to MTX termination ($\beta=9.0$, $p<0.05$), while the youngest

Table 4: Cox proportional hazards regression model for the "Days to treatment"

Variables	coef	se(coef)	Z-value	P-value sig.
Gender (Male)	0.062	0.165	0.375	0.708
Age groups (41- 65 years)	-0.546	0.294	-1.858	0.063
Age groups (65+ years)	-1.319	0.390	-3.378	*0.001
Age on diagnosis groups (20,40)	0.688	0.556	1.238	0.216
Age on diagnosis groups (40,60)	1.459	0.591	2.470	**0.014
Age on diagnosis groups (60,80)	2.236	0.667	3.353	***0.001

Score (logrank) test = 27.11 on 6 df, $p < 0.01$ The significant results ($p < 0.05$) are indicated as *p-value for Age groups (65+ yrs.), **p-value for Age on diagnosis groups (40,60), and ***p-value for Age on diagnosis groups (40,60).

Table 5: Cox proportional hazards regression model for the "Days to MTX termination"

Variables	Coef	Z-value	P-value sig.
Gender (Male)	-0.611	-1.617	0.106
Age groups (41-65yrs.)	-2.026	-2.796	*0.005
Age groups (65+ yrs.)	-5.383	-4.907	**9.23E-07
Age on diagnosis groups (20,40)	2.712	2.528	***0.011
Age on diagnosis groups (40,60)	4.647	3.806	****0.000
Age on diagnosis groups (60,80)	9.068	5.432	*****5.57E-08
First †MTX dose (12.5/W)	0.927	0.77	0.442
First MTX dose (15/W)	1.846	1.574	0.115
First MTX dose (20/W)	1.829	1.497	0.134
First MTX dose (22.5/W)	NA	NA	NA
First MTX dose (25/W)	NA	NA	NA
First MTX dose (30/W)	0.856	0.542	0.588
First MTX dose (7.5/W)	1.347	1.145	0.252
Comorbidity (None)	0.097	0.232	0.816
Comorbidity (Single comorbidity)	-0.578	-1.39	0.164
Other ‡DMARDs (§LEF)	-0.291	-0.234	0.815
Other DMARDs (¶MMF)	-0.164	-0.089	0.929
Other DMARDs (None)	0.022	0.018	0.986
Other DMARDS (Rituximab)	NA	NA	NA
Other DMARDs (††SSZ)	0.051	0.042	0.967
Other DMARDs (SSZ, LEF)	-0.533	-0.432	0.666
Other DMARDS (SSZ, MMF)	NA	NA	NA
Complications of disease (‡‡GERD)	NA	NA	NA
Complications of disease (Multiple bone deformity)	-1.306	-0.928	0.353
Complications of disease (Necrotizing autoimmune myopathy)	1.605	1.000	0.317
Complications of disease (Nodular rheumatoid disease)	-1.342	-1.003	0.316
Complications of disease (None)	0.1789	0.205	0.838
Complications of disease (Osteoporosis)	2.033	1.515	0.129
Complications of disease (Panniculitis, Ruptured Baker Cyst)	2.927	1.851	0.064
Complications of disease (§§RA – ¶¶ILD)	NA	NA	NA

Note: Score (logrank) test = 60.72 on 24 df, $p < 0.01$ The significant results ($p < 0.05$) are indicated as *p-value for Age groups (41-65yrs.), **p-value for Age groups (65+ yrs.), ***p-value for Age on diagnosis groups (20,40), ****p-value for Age on diagnosis groups (40,60), and *****p-value for Age on diagnosis groups (60,80). †Methotrexate; ‡Disease-modifying antirheumatic drugs;§Leflunomide; ¶Mycophenolic acid; ††Sulfasalazine; ‡‡Home conditions; §§Rheumatoid arthritis; ¶¶Interstitial lung disease.

age group (20,40) were least likely to experience fewer days to MTX termination (β=2.7, p<0.05) as shown in Table 5.

Discussion

In RA, medication adherence is highly variable and typically suboptimal, with reports of adherence to conventional Disease-Modifying Antirheumatic Drugs (DMARD) ranging from 22% (underuse) to 107% (overuse)[18]. Also given the prevalence of MTX use and its usage in combination treatment with other agents including increasingly with biologics, it is important to understand factors that may cause patients to be non-adherent or to discontinue MTX treatment[17,20,21].

In our study, the large majority (65.7%) of patients continued with MTX either alone or in combination with MTX & SSZ, MTX & LEF, and the triple combination of MTX/SSZ & LEF being the most prevalent. Two causes of MTX termination dominated this sample, high disease activity, ineffectiveness (30.4%) and GIT toxicity, nausea and vomiting (25.3%). Other factors for MTX termination included non-compliance (11.4%), lung toxicity, pregnancy related and liver toxicity.

While only 10% of our study population had complications of their disease, the most common being osteoporosis and GERD. Continuation of MTX therapy was the rule including all the patients with GERD. The presence of a comorbidity was not a predictor of the duration of MTX treatment. Those with a single comorbidity were marginally more likely to continue with MTX treatment compared to patients with multiple comorbidities. The most common starting dose for MTX in our study was 15mg/week. Older patients usually commenced with 12.5mg/week, rarely 20mg. While the starting dose of MTX was not in itself a predictor for MTX retention patients receiving the higher starting dose of 20mg/week were more likely to continue with treatment.

Gender was not associated with MTX retention rates although females were slightly more likely to continue with treatment and males were slightly more likely to discontinue treatment. There were no differences at all in terms of age; and results indicate that there were no differences between age at diagnosis and MTX retention rates. The same applies to duration of treatment, but patients with a longer treatment duration are more likely to continue with treatment.

A statistical association between two variables merely implies that knowing the value of one variable provides information about the value of the other. It does not necessarily imply that one causes the other[18], hence the following sections use survival analysis to compliment the association results.

Predictors of days to MTX termination

In this study, reasons for MTX termination were classified as AEs, ineffectiveness, non- compliance, and pregnancy related. A previous narrative review found no clear pattern in factors that influence medication adherence in patients with RA[17]. The Cox proportionate results indicate that the age group of patients was a significant predictor of days exposure to MTX termination (duration of MTX treatment). These results imply that days to MTX termination (duration of MTX treatment) increased with age group). Additionally, MTX termination decreased with age as chances of exposure to MTX termination among those diagnosed at age 40-60 years was 4.6 times, and least among those diagnosed at age 20-40 years. Given the prevalence of MTX use and its usage in combination treatment with biologics, it is important to understand factors that may cause patients to be non-adherent or to discontinue MTX treatment[16,19,20].

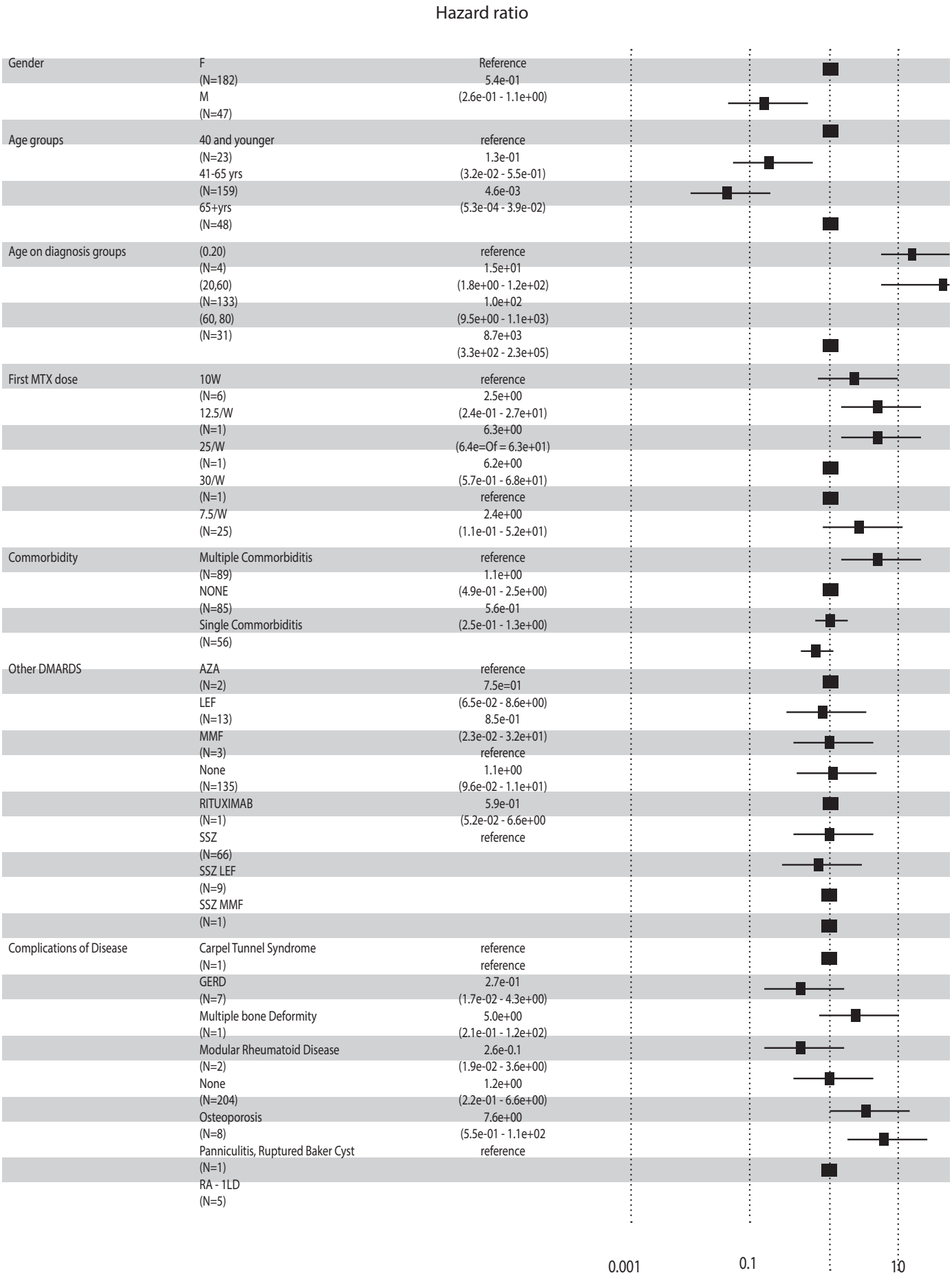
This study provides evidence that MTX dose was not a predictor of duration of treatment (months). However, the study findings highlight that the initial MTX dose was likely to occur between 15 and 20mg/week. In addition, comorbidity was not a predictor of duration of MTX treatment. The results, however, provide clinically relevant insights that those with a single comorbidity were less likely to have a shorter treatment duration, compared to those who had no comorbidity. Further results indicate that all categories of other DMARDS did not predict duration of treatment in this sample. Complications of disease categories were not significant predictors of duration of MTX treatment. Studies suggest that three complications (Panniculitis, Ruptured Baker Cyst, and Osteoporosis) had between 2-3 times greater possibility of increasing the duration of MTX treatment. In contrast, multiple bone deformity complications decreased MTX treatment duration by as much as 1.3 times. Despite these results, it should be noted that MTX is recommended as a first-line treatment in patients with active RA[19], and comorbidity and other DMARDS could be important factors to consider.

Predictors of duration of MTX treatment (Table 5)

The Cox proportionate Hazard results indicate that the older the patient, the more likely they were to remain on MTX treatment. In comparison, younger age groups are more likely to be exposed to shorter treatment duration (Appendix Figure 1).

The Cox proportionate Hazard results indicate that the older the patient, the more likely they were to remain on MTX treatment. In comparison, younger age groups are more likely to be exposed to shorter treatment duration.

Figure 1: A graphical representation of the 'days to MTX termination'



#Events: 75; Global p-value (Log-Rank): 1.8509e-05
AIC; 488.03; Concordance Index 0.78

Limitations and potential shortcomings

The main limitations of this study are its retrospective single-center design. Furthermore, this study did not include demographic factors such as marital status, education level, and other socioeconomic factors, and we could not assess corticosteroid use. Other important factors such as HIV and TB were also not assessed in this study. Lastly, this sample is most unlikely to be a representative of the general population. However, it included a relatively large number of patients who underwent MTX treatment in tertiary level referral hospitals.

Conclusions and recommendations

This study observed that demographic and clinical factors were not significant predictors of MTX adherence. The study provides evidence that age group was a predictor of clinical outcomes with regards to RA. The duration of MTX treatment correlated with increased age. Further results indicate that those who were aged above 65 years, were twice as likely to have multiple comorbidities, and those with multiple commodities were more likely to continue with treatment.

The retention rate for MTX is 65.7%. Adverse events were the most common reason for MTX termination among South African RA patients at TBH, followed by ineffectiveness. Two causes of MTX termination dominated this sample, high disease activity, ineffectiveness (30.4%) and GIT toxicity, nausea and vomiting (25.3%). Other factors for MTX termination included non-compliance (11.4%), lung toxicity, pregnancy related and liver toxicity. The fact that MTX has a high retention rate is encouraging, as it remains the anchor drug among DMARDs in the treatment of RA in resource constrained settings like SA.

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The Maritime Silk Road: case report of Neuro-Behçet's disease from Somalia with positive HLA-B51 haplotype

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Abstract

Behçet's Disease (BD) is a multisystemic inflammatory disorder that commonly presents with oral and genital ulcers and uveitis, and can involve the nervous system i.e. Neuro-Behçet's Disease (NBD). We present the first reported case of Neuro Behçet's Disease (NBD) in a patient of Somali origin. A 34-year-old female from Somalia who had initially presented with headaches and Generalized Tonic-Clonic Seizures (GTCS) but was lost to follow-up. She represented with additional headache, neuropathic leg pain and ulcerated leg swellings with genital itching. Physical examination revealed hyperpigmentation and erythema nodosum on the lower limbs. Laboratory investigations revealed elevated ESR, positive HLA-B51 and a positive skin pathergy test. MRI brain scan revealed non-enhancing white matter hyperintensities in the right meso-diencephalic junction classical for NBD. She was commenced on immunosuppressive therapy with good response at one month. In conclusion, NBD is rare in sub-Saharan Africa. Our case report highlights that the disease is prevalent also on the Maritime Silk Road which includes Somalia.

Key words: Behçet's disease, Neuro-Behçet's disease, Sub-Saharan Africa, Somalia

Introduction

Behçet's Disease (BD) is a multi-systemic inflammatory disorder that usually affects those aged between 20 to 50 years[1]. The prevalence has traditionally been thought to be highest in regions along the ancient 'Silk Road' trading route from the Middle East, but BD is now known to occur in populations far outside this geographical area[2], including along the seldom-known maritime route which extends to the Horn of Africa. The point-based diagnostic criteria for BD include: recurrent oral and/or genital ulceration; ocular lesions; mucocutaneous lesions; vascular lesions; and/or a positive pathergy test[1]. Neurological involvement can occur in approximately 5% of patients with BD i.e. Neuro-Behçet's Disease (NBD), and is defined as BD with additional neurological symptoms in clinical patterns known to occur in BD[3]. NBD usually occurs in the first 5 years of established BD, and can involve the central and/or the peripheral nervous system(s)[3].

Little is known about NBD in indigenous African populations. Severe meningo-encephalitis was found to be more common in Afro-Caribbean patients in the Guadaloupe archipelago[4]. In multi-ethnic European countries, NBD is found to be more common in males with BD from North Africa[5,6], these findings have been consistently shown in indigenous cohorts e.g. from Tunisia and Morocco, where the commonest manifestation of NBD was cerebral venous sinus thrombosis[7,8]. A study from Libya showed that neurological involvement occurs earlier and more frequently in BD patients[9].

There are very few reports of NBD from sub-Saharan Africa (SSA), but they show similar findings of male preponderance. A case series from Senegal found the majority with NBD had parenchymal complications of rhombencephalitis[10], similar to the Caribbean study; however, headaches are also the main presenting feature in NBD from West Africa[10,11]. The only published reports from East Africa come off the coast from Comoros: in addition to echoing findings from the rest of the continent, one-third had severe disability or death due to NBD[12]. Over-arching all these reports from Africa is the significant absence of the HLA-B51 haplotype, which has the highest genetic susceptibility and is associated with more severe BD[13]. There are no published reports of HLA-B51 positive individuals from the East Africa region.

We present the first reported case of NBD in a patient of Somali origin, who also carried the HLA-B51 haplotype, who we diagnosed and managed at our tertiary regional referral centre in Nairobi, Kenya.

Case report

A 34-year-old female from Somalia first presented to our facility five years before with headache. Magnetic Resonance Imaging (MRI) of the brain was reported to show non-specific White Matter Hyper-intensities (WMHs). She was commenced on medication but was very soon lost to follow-up when she returned to her home country.

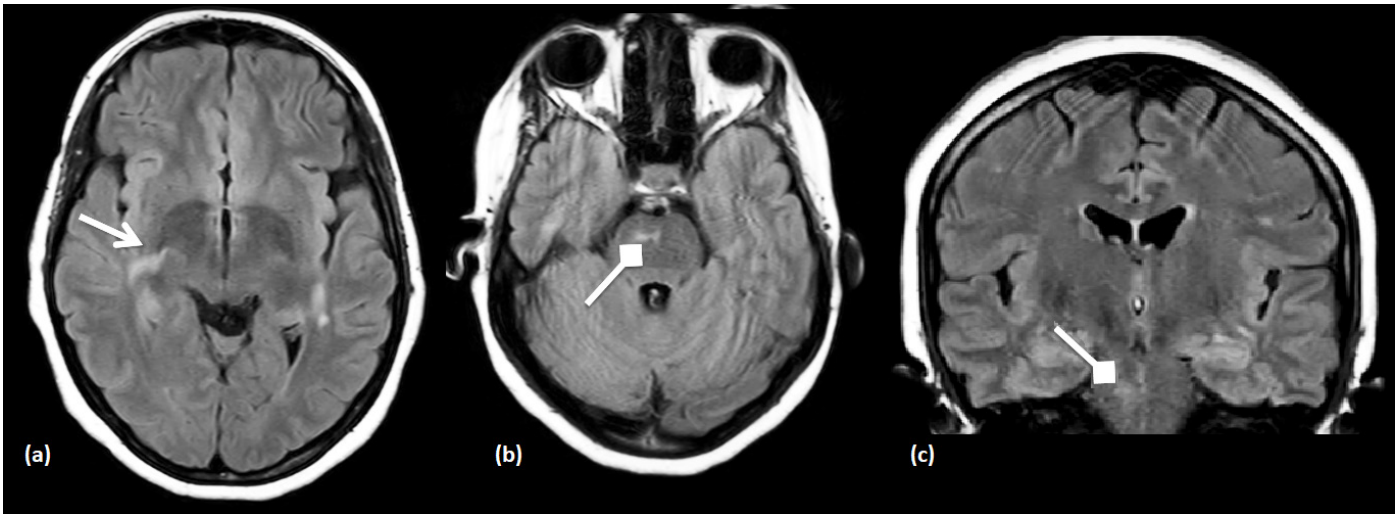
Five years later, she was admitted to our hospital as an emergency due to one year of worsening headaches, but also frequent Generalised Tonic-Clonic Seizures (GTCS), new pains in her lower limbs and depressed mood for six months. On further clinical evaluation, she also confessed to having ulcerated swellings of the lower limbs for six months, genital itching, and occasional mouth ulcers. She commented that she would develop large blisters on her hands following intravenous cannulations in Somalia when she was admitted sometimes for GTCS.

Physical examination revealed erythema nodosum on the shins. Neurological examination demonstrated reduced reflexes in the lower limbs with stocking distribution loss of sensation to the mid-shin level, in keeping with peripheral neuropathy. Gynaecological examination confirmed vulvo-vaginal ulcers. Ophthalmological examination was normal.

Blood tests, including full infective, metabolic, vasculitic and auto-immune panels, were all normal except for raised white cell count of 12.9 x 10^9/L, elevated Erythrocyte Sedimentation Rate (ESR) of 130 mm/h (normal <20) and C-Reactive Protein (CRP) of 109.6 mg/L (normal <5). Chest radiograph was normal.

We suspected BD, and proceeded to do a skin pathergy test which was positive, and further requested for HLA-B51 haplotyping which also came back positive, confirming the diagnosis. We did not organise neurophysiological testing due to the leg ulcerations and pain. Repeat MRI brain scan showed worsening WMHs, but now with involvement of the right meso-diencephalic junction and pons without vascular involvement (Figure 1), all pathognomonic of NBD.

Figure 1: Fluid-Attenuated Inversion Recovery (FLAIR) MRI sequences of the brain: (a) coronal, (b) axial, and (c) coronal slices showing meso-diencephalic junction (open arrow) and pontine (diamond arrows) white matter hyper-intensities pathognomonic of neuro-Behçet's disease.



For NBD we initiated immunosuppressive therapy with azathioprine at 2.5mg/kg/day, prednisolone at 1mg/kg/day, and colchicine 0.25mg three times a day. Her seizures were controlled with carbamezapine 200mg twice a day, which we slowly increased to 300mg twice a day after a week, and her neuropathic pain was controlled with pregabalin 150mg twice a day. She was reviewed by the inpatient psychiatry team and commenced on mirtazapine 15mg nocte for her depression. She also underwent inpatient physiotherapy and counselling.

We reviewed her as a Multi-Disciplinary Team (MDT) after one month. She was remarkably better with resolution of most of her debilitating symptoms. She had no more headaches and had had no more seizures, and her skin lesions healed had healed well. Repeat ESR and CRP were now in normal range.

Discussion

This case fulfilled the international diagnostic criteria for NBD[3]. She presented with headache, seizures and neuropathic pains almost in tandem with the new diagnosis of BD. This contrasts with the average time usually taken from onset of BD to NBD[7,14]. It is possible that the first presentation to our facility with headaches could have been the onset of NBD, and the systemic features were not clinically evident. Primary headache disorders are common in NBD patients[15], and up to 20% of BD patients can first manifest as NBD, which is a possibility for our patient too[16]. Cutaneous manifestations were important in clinching the diagnosis clinically in our patient; erythema nodosum is more prevalent in female patients with BD[13] but can often be missed.

The HLA-B51 allele positivity in our case is unique when compared to the overwhelming number of negative cases reported across SSA[4,10]. Putatively, the proximity of Somalia to the traditional Silk Road could explain this finding. Having this haplotype is also associated with more severe disease as presented in our case[3].

The MRI findings in our patient were also pathognomonic for NBD. Studies from North Africa have shown that deep white matter and subcortical structures are most affected, followed by the brainstem and pons, and then the spinal cord[17]. We did not manage to scan the spinal cord of our patient, although clinically she did not have a myelo- or radiculo-pathy. Some patients with NBD in SSA have been reported to have more tumefactive lesions mimicking brain tumours, including of the pons[18,19].

Our patient had good outcomes as treatment was directed by the MDT, and therapy followed the international guidelines for the management of NBD[20]. In our case, given the moderate burden of disease, we added azathioprine on top of the usual regimen of corticosteroids and colchicine. We kept in mind the child-bearing age of the patient in our choice of immunosuppression, otherwise we would have considered more efficacious treatments such as infliximab.

In conclusion, our case is unique in the published literature of NBD in SSA in that she was a female, from a lesser-known part of the Silk Road, had positive HLA-B51 haplotyping, and had both central and peripheral nervous system involvement. Additionally, the MRI brain findings and cutaneous manifestations were important in making the timely diagnosis so as to allow immediate and appropriate treatment, which led to good outcomes.

Declarations

Ethics approval and consent to participate

This manuscript fulfilled our institutional criteria for exemption from full Institutional Ethics Review Committee evaluation. The patient gave informed written consent for her anonymised case history and images to be published, and this consent form is filed in her medical file.

Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Competing interests

The authors declare that they have no competing or conflicts of interests.

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Synovial lipoma arborescens: Case report

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Abstract

Synovial Lipoma Arborescens (LA) is a rare disease, affecting usually the knee joints. The case presents a 69-year-old male complaining of a left knee swelling of 9 months duration for which he sought multiple medical and orthopaedic advices without improvement or diagnosis. Diagnosis was done by characteristic MRI imaging of this benign tumour. In conclusion, synovial lipoma arborescens is rare but should be kept in the differential diagnosis of knee swelling

Introduction

Synovial lipoma arborescens is a rare condition affecting synovial linings of the joints and bursae, with "Frond-like" deposition of fatty tissue. It accounts for less than 1% of all Lipomatous lesions[1]. Patients typically present in the 5th-7th decades, but the condition has also been reported in the young[2]. The clinical presentation is of joint swelling, variable arthralgia, and frequently an associated effusion[3]. Many patients have associated pathologies. Described associated pathology in the knee include[4] degenerative changes, meniscal tears, and joint effusion. MRI is the modality of choice for diagnosis. A typical appearance is of fat containing frond-like synovial mass, usually outlined by concurrent joint effusion. The lesion follows the signal intensity of fat on all sequences.

Case report

A 69 year old Libyan male patient presented to the outpatient rheumatology clinic complaining of 9 months history of left knee swelling. At the start of his illness, he went to several orthopaedic doctors. The basic investigation was done and revealed normal CBC, raised CRP (6.5 mg/dl), normal ESR (25 mm/hr), negative rheumatoid factor, and normal uric acid. One month later, arthroscopy was done which showed a meniscal tear, and therapeutic arthroscopic intervention was done. After two weeks his left knee joint swelled again and was treated by intraarticular steroid injection (Depomedrol 40mg) then the patient was advised to commence physiotherapy. After two months, the patient sought another opinion from another doctor who diagnosed rheumatoid arthritis with monoarticular presentation and treated with prednisolone tablet 20mg once daily with gradual tapering to 5mg once daily and leflunomide tablet 20mg once daily. This treatment was stopped by the patient after 2 months because no improvement occurred. MRI of the left knee was done during this period; the radiologist noted a menisci going with generative changes of the knee (osteoarthritis). Another doctor described NSAIDs and glucosaminoglycans without improvement.

In February 2021, when he presented to our clinic he had a clinically swollen left knee. In the MRI, and there was a fatty tissue in suprapatellar area and a second opinion was sought from another radiologist. The report was ready on the second day, and it revealed knee joint effusion with many synovial fronds demonstrate T1WI, T2WI hyperintensity which suppressed on fat saturation sequences, a picture compatible with lipoma arborescens (Figures 1 and 2).The patient was referred to an orthopaedic doctor for total synovectomy.

Figure 1: T1W1 image

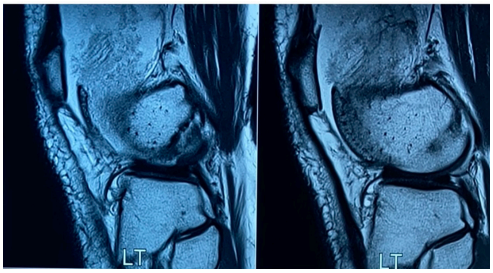
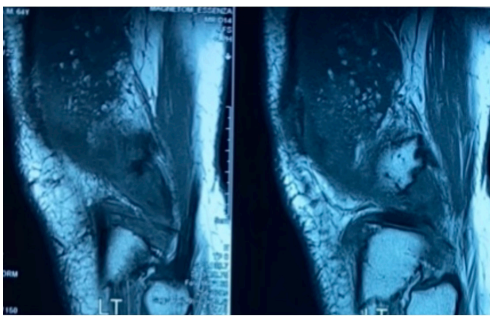


Figure 2: T2W1 image



Discussion

Lipoma Arborescens (LA) is a rare, intra-articular benign lesion of the synovium[5]. The first detailed case report was done by Arzimanogluin in 1957[6]. Since then, less than 200 cases have been reported in the literature by 2017[7]. Most reports consist of just one case or a small series of this unusual lipoma, while Howe and Wenger[8] described the largest series with 45 lesions in 39 patients. Aymen *et al*[9] reported a case of LA in a 47 year old patient who received arthroscopic synovectomy at Monastir University Hospital, Tunisia. They also described unilateral knee involvement as typical while atypical cases include both knees and involvement of other joints, such as shoulder, elbow, wrist, hip, and ankle[8,10,11-14].

Patients complain of chronic, progressive, painless swelling of the involved joint. Effusion is almost always present but limitations in range of movement and pain are not seen very often[11,15,16]. MRI is the diagnostic imaging modality of choice and can demonstrate variable morphological patterns with pathognomonic characteristics[15,17].

A large frond-like mass arising from the synovium is seen, with signal intensity similar to fat on all pulse sequences[18,19,20]. Alternatively, multiple villous proliferations of the synovium and fatty appearing globules can be seen, while mixed patterns can also appear[19].

LA is a benign tumour, so a biopsy is not regarded by some authors as an essential part of the treatment algorithm. Recommended treatment is open synovectomy[15,21-23] and recurrence after surgery is uncommon[21]. When synovectomy is delayed more than a year from symptoms onset, early osteoarthritis may develop[24].

Another diagnosis as synovial chondromatosis, pigmented villonodular synovitis, quadriceps fat pad impingement, synovial haemangioma, and intra-articular liposarcoma may mimic LA and cause confusion[25,26].

Tuberculous arthritis is one of differential diagnosis of chronic knee swelling especially in Africa. Tuberculosis is endemic in certain areas such Asia, the middle East, and Africa[27].

Skeletal involvement is seen in 1-3% of patients with tuberculosis and for approximately 10-11% of extrapulmonary cases. Among them, approximately one half of these affect the spine and the rest are extraspinal affecting mainly hip and knee joints[27].

Conclusions

LA is a rare benign lesion that commonly affects the knee joint, especially in suprapatellar pouch and we should keep it in our mind as a differential diagnosis of chronic knee swelling to avoid a delay in diagnosis as occurred with our patient and also the patients in other case series.

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Severe lupus enteritis, diagnosis and treatment journey: case report

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Abstract

Gastrointestinal system involvement is reported in a patient diagnosed with severe Systemic Lupus Erythematosus (SLE). Lupus enteritis is quite uncommon and characterized by presence of abdominal pain, nausea, vomiting and diarrhoea. The main pathological insult arises from inflammation of mesenteric vascular territories. Diagnosis of lupus enteritis is dependent basically on clinical, biochemical, serological and radiological features and one needs to rule out other differentials like infectious process or medications' side effects. The most critical step in management is to exclude acute surgical condition followed by supportive measures, antibiotics and immunosuppressive drugs. In this report, we will discuss a case of a patient diagnosed with SLE through the gate of lupus enteritis.

Keywords: Systemic Lupus Erythematosus, Lupus Enteritis, Gastrointestinal system, Female, Saudi Arabia

Introduction

Systemic Lupus Erythematosus (SLE) is considered an immune complex mediated disorder characterized by relapsing and remitting phenomenon with an inflammatory autoimmune background[1]. It usually affects young, child bearing age women with a 9:1 female to male ratio[2].

SLE can attack different organs resulting in devastating complications if not diagnosed early and treated according to the organ affected[3]. Gastrointestinal complaints are frequently noticed in 40-60% of lupus patients and these symptoms could be related to either side effects of medications or attributed to infectious triggers or severe lupus activity. Lupus – related gastrointestinal symptoms occur in about 42.5% of patients diagnosed with lupus and there is a wide spectrum of manifestations that might present and affecting the prognosis of disease[4]. In this case report, we will describe a young female patient who presented with mainly gastrointestinal (GI) manifestations and labeled at the end as a case of SLE.

Case report

The patient was a 21 year old female, not known to have any medical illness before, she presented to the Emergency Room (ER) Department at King Fahad Medical City in Riyadh (KFMC) with a history of: diffuse abdominal pain that was moderate in severity, nausea and vomiting. The symptoms made the patient unable to tolerate oral food and liquids for the last four days. She was also complaining of diarrhoea which was watery in nature, moderate to large amount, the diarrhoea was not associated with fresh blood. Upon admission in (ER), the patient's vitals were; blood pressure 138/82, her heart rate 108, respiratory rate 19 and she was not febrile with core temperature 36^0C.

The patient was admitted under the internal medicine team for rehydration and further work-up. There was no history suggestive of any systemic symptoms like fever, fatigability or weight loss. No history of any cardiovascular or respiratory symptoms. Other systemic review including family history was completely unremarkable except for arthralgia which started two months earlier, the arthralgia was not associated with morning stiffness, not associated with certain activities and did not hinder the patient from carrying out her usual activity.

During the patient's admission, we were consulted for our opinion regarding her GI manifestations and arthralgia. Upon examination, the patient looked pale and sick with acceptable vital signs except for a high blood pressure reading of 150/92. No rashes were observed on the patient's face or body, she had no oral or nasal ulcers and there was no synovitis. Abdominal examination was performed and the patient had diffuse abdominal tenderness with positive bowel sounds. All other organ examinations were unremarkable.

Figure 1: This is CT- scan of abdomen and pelvis with contrast done for the patient upon her presentation to ED department: The blue arrow is showing bowel wall thickening indicative for inflammatory process while the arrow in the black colour showed an area of free fluid due to general pathological condition (Infections/Inflammatory process are differential diagnoses)

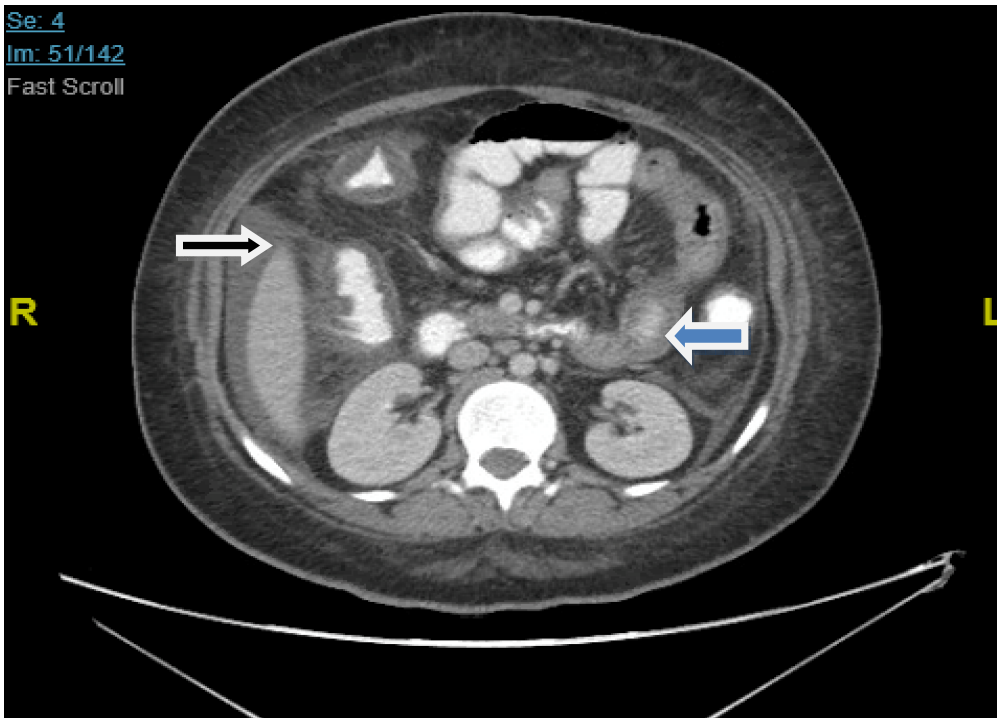

Table 1: Laboratory investigations done to our patient since her presentations and during the follow-up visits in our clinic

Labs	At presentation	After 3 months	After 6 months	After 9 months
Urea (mmol/L)	4 mmol/L	5.4 mmol/L	6.6 mmol/L	4.7 mmol/L
Creatinine (mcmol/L)	75 mcmol/L	54 mcmol/L	56 mcmol/L	60 mcmol/L
Proteinuria (g/day)	1.5 g/day (high)	0.14 g/day	0.30 g/day	0.20 g/day
*WBC	5.4 10*3/µL	4.18 10*3/µL	3 10*3/µL (low)	2.8 10*3/µL (low)
Platelets count	251 10*3/µL	291 10*3/µL	312 10*3 /µL	385 10*3/µL
Lymphocyte count	0.51 10*3/µL (low)	0.70 10*3/µL (low)	0.58 10*3/µL (low)	0.65 10*3/µL (low)
Haemoglobin	9.1 g/dl (low)	11.6 g/dl	12 g/dl	12.1 g/dl
*MCV	73.1 fl (low)	78.9 fl	80.9 fl	78.7 fl
*C3	0.65 g/L (low)	1.4 g/L	1.1g/L	0.60 g/L (low)
*C4	0.04 g/L (low)	0.3 g/L	0.2 g/L	0.14 g/L
*ANA	Positive			
*DsDNA	1325 IU/ml (high)	28.6 IU/ml (high)	21.2 IU/ml	19.1 IU/ml

*WBC= White blood cells, *MCV= Mean corpuscular volume, *C3,4= Complements
*ANA= Antinuclear antibody, *DsDNA= Anti double strand DNA

The patient underwent an extensive investigation which showed: Leucopenia of 2.9 10*3/µL with an anaemia of chronic disease 9.1 g/dl with a mean corpuscular volume of 73.1 fl and normal count of platelets. Renal and hepatic profiles were normal. Serum amylase and lipase values were also normal. Full septic screen ordered and cultures turned out to be negative without any evidence of infection. Urinalysis showed positive WBCs, positive RBCs and +2 protein. Also, Antinuclear Antibodies (ANA) were done and it was positive. Anti-double-stranded DNA antibody was elevated 1325 IU/ml while the complement (C3) value was low 0.65 g/L. ANCA test was negative. 24hour urine protein collection had shown proteinuria with 1.5 g/day.

CT-scan for abdomen and pelvis was arranged and it showed diffuse small and large bowel wall thickening suggestive for inflammatory process with mild-moderate free fluid. The gastroenterology team offered to do an upper and lower GI endoscopy but the family was hesitant to proceed for any endoscopic intervention. While we

were waiting for the result of remaining labs, the patient was managed by supportive measures such as: IV fluid, bowel rest, anti-emetics and proton pump inhibitors as advised by GI team.

Due to presence of proteinuria, the patient underwent a renal biopsy and the result was: Class III lupus nephritis, no crescents or interstitial fibrosis or tubular atrophy. Upon exclusion of infections, the patient was started on methyl prednisolone 60mg IV once a day and the patient was offered the choice between cyclophosphamide and mycophenolatemofetil (MMF), benefits and side effects and treatment regimen of both drugs were explained to the patient, the patient and her family both refused cyclophosphamide and opted for MMF which was started with the optimal dose gradually reached of 1.5gm orally twice a day. The patient was reviewed daily after starting this regimen and unfortunately the patient was still complaining of cramping abdominal pain with intractable vomiting that had led to multiple episodes of severe hypokalemia with potassium levels of 3.2 moll/L, 2.8 moll/L and severely reduced level of potassium 2.3 moll/L subsequently over a duration of two weeks. Given the seriousness of her hypokalemic episodes and the lack of significant improvement in her GI symptoms we re-discussed the importance of early and aggressive treatment of her condition and the ultimate decision of using cyclophosphamide was reached.

Intra venous cyclophosphamide (EUROLUPUS) protocol of 500 milligrams every two weeks for a total of six doses followed by maintenance therapy with MMF was started. The patient's vomiting episodes and abdominal pain improved within two days of the first cyclophosphamide dose and within one week the patient was discharged home on oral steroids with a tapering plan, hydroxychloroquine 400 milligram daily, lisinopril 5 milligram daily, calcium and vitamin D supplementations and follow up appointments in the Day Care unit and Rheumatology clinic. Upon follow-up as an outpatient, the patient's gastrointestinal symptoms had improved significantly and proteinuria levels were showing complete remissions.

Discussion

Lupus enteritis is a not uncommon sequela of SLE with worse prognosis arising from immune complex insult with activation of the complements' system leading to vasculitic injury and sub mucosal inflammation[5]. Gastrointestinal manifestations due to active lupus disease are wide and varied and this patterns can include: enteritis, vasculitis, pancreatitis, protein-losing enteropathy, intestinal pseudo-obstruction and peritonitis[6]. Gastrointestinal symptoms suggestive for lupus enteritis are non- specific as patients can present to emergency department with different vague presentations. So, the differentiation between various processes responsible for such symptoms is not an easy process as the differential diagnoses are broad and can include: adverse events from immunosuppressive drugs, or related to infectious organisms like bacterial, fungal or viral infections and if all these possibilities have been excluded; lupus enteritis will be the most suitable diagnosis.

There are many cases reported in literature about lupus enteritis and the most frequent symptoms noticed are abdominal pain followed by nausea, vomiting and diarrhoea[7].

The diagnosis of lupus enteritis is not dependent on tissue examination as in many conditions that biopsy will not be a feasible option and radiological imaging with Computerized Tomography Scan (CT scan of abdomen and pelvis) would be the gold standard for reaching the diagnosis[8]. There are three main radiological abnormalities reported to be correlated with presence of enteritis: (i) bowel wall thickening with edema > 3mm and this is called "target sign", (ii) engorgement of mesenteric vasculatures suggestive for vasculitis, (iii) change in enhancement of intra-abdominal fat. Moreover, other radiographic modalities can be utilized to clarify if there is any enteric inflammation like: conventional angiography and Magnetic Resonance Angiogram (MRA). Pathological examination can be done by requesting assistance from the gastroenterology team to do endoscopic intervention with biopsy that will show evidence of bowel wall mucosal hyperemia or ulceration noticed predominantly in jejunum, ileum followed by colon[9].

Severe gastrointestinal syndromes related to lupus occur mostly in the context of active general disease, but we cannot assume that for all cases as some patients can present with lupus - related GI complications with low (SLEDAI) based on contradiction noticed between different studies[10]. However, checking for other major organ involvement among lupus patients presenting with GI symptoms is desired to tailor the plan regarding which therapy should be administered. There is no single laboratory bio - marker that can be used to diagnose GI complications in lupus. Haematological abnormalities like: anaemia of chronic disease, leucopenia and thrombocytopenia all can be seen in these patients[11].

Additionally, lab tests for lupus activity such as: low complements level with an increment in the level of anti double-stranded DNA antibodies are noticed among patients diagnosed with lupus- related GI manifestations[12]. Positivity of anti-phospholipid antibodies is reported in 28% of individuals presenting with GI syndromes[13]. Ruling out other major organ involvement is paramount as nephritiscarditis and neuropsychiatric events might occur with gastrointestinal symptoms concomitantly[14].

There is no single therapeutic plan that can be followed for managing patients with lupus related GI symptoms. The most important step in management is to exclude surgical abdomen with a picture of bowel perforation before initiation of any immunosuppressive drugs[15]. The treatment mainly depends on supportive measures like: surgical team consultation, IV fluid, bowel

rest, antibiotics till the infections are ruled out then immunosuppressive medications can be initiated[16].

The mainstay immunosuppressive therapeutic agent is glucocorticoids therapy IV/ oral routes. Another immunomodulatory agent can be added like: Cyclophosphamide (CYC), Mycophenolate Mofetil (MMF), Azathioprine or Rituximab (RTX)[17,18].

Early discovery of lupus related gastrointestinal complication is essential as the initiation of steroid and immunosuppressive agents like intravenous cyclophosphamide will prevent unfavouarable outcome[19].

Lupus - related GI complications carry a higher risk for relapse especially among patients who have bowel wall thickening more than 9mm in (CT scan) and patients who received lower cumulative dose of glucocorticoids[20].

Alshehri *et al*[21] reported one case from Saudi Arabia diagnosed with SLE after her presentation with symptoms of abdominal pain and diarrhoea with picture of mesenteric involvement shown in CT-abdomen and pelvis.

Conclusions

Gastrointestinal symptoms among patients with lupus are frequently seen, however the symptoms related to (SLE) flare are associated with poor prognostic outcomes. The diagnosis depends mainly on the clinical picture with supportive radiological evidence after excluding other diagnoses like infections. The management of such complications has two components: The first is: IV fluid/ bowel rest after excluding worrisome conditions such as bowel perforation while in the second the treatment will encompass glucocorticoid therapy plus another immunosuppressive lines.

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