Research article

Clinical profile of lupus erythematosus in Nigerian males

Ayanlowo O[1], Kamal M[1], Ima-Edomwonyi U[1], Akinkugbe A[1], Otrofanowei E[1], Olaosebikan H[2], Adelowo O[1,2]

[1]Department of Medicine, Faculty of Clinical Sciences, College of University of Lagos/ Lagos University Teaching Hospital, Lagos, Nigeria
[2]Department of Medicine, Lagos State University College of Medicine/Lagos State University Teaching Hospital, Lagos, Nigeria

Corresponding author:
Dr. Hakeem B. Olaosebikan, Department of Medicine, Faculty of Clinical Sciences, College of University of Lagos/ Lagos University Teaching Hospital, Lagos, Nigeria. Email: hakeemolaosebikan37@gmail.com

Abstract

Background: Systemic Lupus Erythematosus (SLE) is a sexually dimorphic chronic autoimmune inflammatory disease affecting multiple organs, characterized by production of autoantibodies against nuclear and cytoplasmic antigens. Like other autoimmune conditions, SLE is more prevalent in females of childbearing age, and very rare in males. Recent evidence implicated the presence of higher genetic risk loads in men. There is strong evidence supporting the contribution of X-linked Toll-like receptor 7 (TLR7) gene polymorphism to the development of SLE with a stronger effect in males than females.

Objective: This study describes the demographic traits, potential risk factors, clinical and laboratory profiles of male lupus patients. The second part is a review of the literature to document the demographic characteristics, possible protective and predisposing factors, pathophysiology and peculiar characteristics.

Methods: We document findings in the five males who presented with SLE (from a cohort of 108 SLE patients) who presented between May 2015 and June 2017.The second part involved a review of the literature on SLE in males to document the demographic characteristics, possible protective and predisposing factors, pathophysiology and peculiar characteristics. The review involved a literature search using PubMed, Medline, Google Scholar, Africa-wide NiPAD and African Journal online.

Results: Most males with SLE present in the third and fourth decades of life. The most common clinical findings are on the skin, joints, renal and haematology systems. Cutaneous lesions include acute cutaneous lupus like malar rash; and chronic cutaneous lupus, associated with hair affectation (non-scarring alopecia). Others include serositis (pericardial effusion); renal impairment leading to chronic kidney disease; neuropsychiatric and haematologic (lymphopaenia) features; and positive serology: elevated antinuclear antibody (values from 1/320 to 1/640), raised anti double-stranded DNA, anti SmAb and low complement level.

Conclusions: Males and females both have the classic lupus symptoms, but other clinical characteristics such as a later onset, a more severe form of the disease, and prognosis appear in males.

Key words: Lupus erythematosus, Nigerian males, Cutaneous lupus, Autoimmune inflammatory diseases

Introduction

Systemic Lupus Erythematosus (SLE) is a sexually dimorphic chronic autoimmune inflammatory disease affecting multiple organs. It is characterized by the production of autoantibodies directed against nuclear and cytoplasmic antigens[1]. It is more common among African Americans and African Caribbeans[1]. Like other autoimmune conditions, SLE is considered a disease of females of childbearing age and is very rare in males. Globally, the male to female ratio is thought to be 9:12. Before puberty, it is 3:1; during the reproductive years, it is 10:1 to 15:1, and after menopause, it is 8:13.

The aetiopathogenesis of SLE is still not fully understood. It is generally considered to result from an interplay of genetic, hormonal and environmental factors, which can also influence the nature and pattern of the disease[4]. Genetic involvement includes the combination of susceptibility genes and the absence of protective genes. Animal studies have shown that estrogens exacerbate, while androgens ameliorate the disease[5].

Reasons for female predilection are not completely understood, though it is believed to be due to endogenous hormonal influence. There is an established connection between high estrogen levels and an increased number of autoreactive B-cells and immunoglobulin, leading to increased autoantibody-mediated pathology in SLE[5]. Other hormonal influences on female predilection include lower plasma androgen levels, hyperprolactinemia, and differences in

gonadotropin-releasing hormone (GnRH) signalling[3]. In addition, females have more of a T-helper[2] predominant immune response, hence, they respond to infections, vaccinations, and trauma with increased antibody production[2]. However, recent studies have not shown any difference in hormonal blood levels of follicle-stimulating hormone, luteinizing hormone, testosterone and oestradiol between men with lupus and men without lupus[6].

Recent evidence has implicated the presence of a higher genetic risk load in men; hence, men require more genetic susceptibility than women to develop SLE[7]. There is strong evidence supporting the contribution of X-linked Toll-like receptor 7 (TLR7) gene polymorphism to the development of SLE with a stronger effect in males than females, causing more severe presentations in males, including renal impairment, central nervous system and vascular diseases[2,8]. TLR7 gene encodes proteins that recognize endogenous RNA-containing autoantigens leading to autoantibody production and expression of type1 IFN which is the major cytokine in the pathogenesis of SLE[8].

In a retrospective private hospital-based study[9], SLE was documented in three males among 66 patients. A similar study conducted in a public tertiary hospital in Southern Nigeria[10], recorded five males with SLE among 52 patients. However, the objective of these studies was not to study the peculiarities of lupus in males. Moreover, the data on the clinical characteristics and peculiarities of SLE in males are limited in Africa. The only study from sub-Sahara Africa is by Dey *et al*[11] They analyzed the clinical characteristics of 13 males with SLE among 134 patients at Korle Bu Teaching Hospital in Ghana. They observed that constitutional symptoms and arthritis were the most frequent manifestations of SLE in their cohort and lupus nephritis was the major early indicator of organ damage[11]. They concluded that the clinical characteristics of males with SLE in their cohort are comparable to reports from other populations.

Although SLE is more common in females, peculiarities in males must be studied: clinical manifestations, outcome, and drug management. Therefore, this study hopes to better understand SLE in males and possible aetiopathogenesis and genetics in the affected.

The case series aimed to document the clinical profile of males with lupus amongst a series of patients at the Rheumatology clinics of Lagos University Teaching Hospital (LUTH) and Lagos State University Teaching Hospital (LASUTH). It will also be reviewing the literature to highlight predisposing factors, peculiar clinical characteristics, treatment, prognosis, and disease activities in males with lupus.

Materials and methods

This was a descriptive study to document the findings in males with systemic lupus erythematosus over 2 years at the rheumatology clinics of two tertiary hospitals (Lagos University Teaching Hospital, LUTH and Lagos State University Teaching Hospital, LASUTH) in Lagos, Nigeria. These hospitals are the main referral centres where Rheumatologist specialist services are available in Lagos. The two institutions are in Lagos State, the economic centre of Nigeria, and the former capital of Nigeria. Lagos state is made up of an indigenous population with well-recognized sub-nationalities that make it a predominantly Yoruba environment, however, she also has other pioneer immigrant settlers. Lagos is best described as a global socio-cultural melting pot. In view of this, the population of Lagos can be described as fairly representative of Nigeria.

The study was in two parts. In the first part, we document findings in the five males who presented with SLE (from a cohort of 108 SLE patients) who presented between May 2015 and June 2017. In this series of men with lupus, this study documented the demographic details and clinical features including immunological findings according to the SLICC criteria for diagnosis of SLE.

The second part involved a review of the literature on SLE in males to document the demographic characteristics, possible protective and predisposing factors, pathophysiology and peculiar characteristics. A literature search was done using PubMed, MEDLINE, Google Scholar, Africa-wide NiPAD and African Journal Online. A medical heading search was done using the following words systemic lupus erythematosus, lupus, and lupus erythematosus in males. Approval from the Ethical Committee of LUTH was obtained before the commencement of the study with HREC number: ADM/DCST/HREC/APP/153.

The data was captured on an Excel spreadsheet and analysis was done using SPSS 22. Descriptive statistics were used to document the frequency, mean and standard deviation. Tables were used to summarize the results.

Results

The males were 4.6% of the total number of patients in the lupus cohorts studied, giving a male-to-female ratio of 1:9. The five men who presented were between 20 and 44 years; the mean age was 31.2 ± 8.3 (SD) years. Four of the men were single and one was married; four of them are from the Igbo tribe (South – East Nigeria) and one was from the South–South part of Nigeria. Two were students, two were junior professionals (business and clergy) and one was semiskilled (trader). Joint pain and swelling were the most frequent presenting symptoms in three of the men, followed by skin rashes, fever, and fatigue in two persons respectively.

The most common clinical signs on examination were on the skin. Acute cutaneous lupus in two, involving malar rash and acute cutaneous lupus; and chronic cutaneous lupus in two (one generalised discoid and one localised discoid lesion).

There was hair affectation in two (non-scarring alopecia). Joint affectation (arthritis) was noted in two men and serositis in one (pericardial effusion). One of the men presented with features of renal impairment (pedal oedema, hypertension, proteinuria 3+) and the definitive diagnosis was chronic kidney disease. Other systemic features were psychosis and numbness (neuropsychiatric) in two; and lymphopenia (haematology) in one. None of the men presented with ocular, cardiovascular and mucosal diseases.

Table 1: Clinical and laboratory profile of lupus in males

S/N	Age (years)	Duration (months)	Skin	Hair (Alopecia)	Painful joints	Serositis	Renal	Neurology	Haematology	Immunology
1	21	4	Malar rash	Nonscar-ring	Yes	Pericardial effusion	No	No	Lymphope-nia	ANA: 1:640 Anti-dsDNA: 76
2	28	1	No	No	Yes	No	Chronic renal failure	No	No	ANA: 1:160 CTD: 5.3 Anti-dsDNA: Positive Low complement
3	29	1	Gener-alized discoid lesion	Non-scar-ring	No	No	No	Psychosis	No	ANA: 1:640 Anti-dsDNA: negative Anti-SmAb: Positive
4	35	6	Leg ulcer	No	Yes	No	Pedal oedema	Numbness	No	CTD positive
5	33	36	Localized discoid	No	No	No	No	No	No	ANA: 1:320 Anti-dsDNA: 1:80

Table 2: Studies on clinical profile of lupus in males

Parameters	Series/ Cohort[1]	Series/ Cohort[2]	Series/ Cohort[3]	Series/ Cohort[4]	Series/ Cohort [5]
Authors/countries	CC Mok *et al*[15] / Hong Kong	Ramírez *et al*[12]/Sweden	Dey *et al*[11] / Ghana	MA Garcia *et al*[6] / Latin America	Hwang J, *et al*[14] / Korea
Frequency (N)	51	166	13	123	53
Age range, Mean/Median Age (years)	31±2.1 SD	40 ± 19	30.62 ± 8 47	29.2 (18.9–36.0)	32.9 ± 13.6
Duration of symptoms in months (Mean/Median)			21.31(0-100+)		
Summary of clinical features (%)					
Skin					
-Malar rash	57	39.2	61.5% rash (not categorized)	28.5	37.7
-Discoid rash	16	18.7	¬ _	5.7	17
-Photosensitivity	20	43.4	_	24.4	13.2
Mucosal	2	15.7	54.5	13	17
Hair	20	-		18.7	22.6
Joint	65	69.9	92.3	66.7	60.4
Serositis	20	56	61.5	7.3	35.8
Renal	35	54.2	38.5	7.3	62.3
Neurology	10	11.4	46.2	0.8	13.2
Hematology	Haematology:16 Lymphopenia:73 Thrombocytopenia: 25 Haemolytic anaemia: 14	60.2	15.4	13.8	83
Immunology					
ANA	98	98.2	91.7	98.3	94.3
-Anti-dsDNA	53	66.1	33.3	78.1	-
-Anti-SmAb	14	15	33.3	48.9	-
CVS	-	-		6.5	
Ocular	-	-	-	-	

Antinuclear antibody (ANA) was elevated in four; with values between 1/320 and 1/640; raised anti dsDNA was found in three men; CTD screening positivity in one; anti-SmAb in one and low complement level in one.

Discussion

SLE is characterized by alternating periods of disease remission and activity and by a variety of clinical presentations, including constitutional features and organ-specific features[1]. This case series of male patients with lupus highlights the varied clinical findings that are known to occur in SLE[1]. We noted multisystemic presentation involving the integumentary, neurological, respiratory, cardiac, renal, haematological and immunological systems.

In general, the features found in males were similar to typical manifestations of lupus in females, however, certain key clinical manifestations were different. These differences include late onset, a more complex and severe form of the disease in terms of clinical presentations and prognosis, but they have a lower rate of relapse[3,12]. LUMINA (Lupus in Minorities, Nature versus nurture cohort), a multinational study, documented Caucasian ethnicity, alcohol use, smoking, lupus anticoagulant positivity and renal involvement as more common in male lupus patients, with less common musculoskeletal features than in the females[13]. Lupus in males presents with more frequent cutaneous manifestations, serositis, cardiorespiratory manifestation, seizures, and peripheral neuropathy, autoimmune haemolytic anaemia and thrombocytopenia, more frequent and severe renal involvement[3]. Ramírez *et al*[12], in Sweden, reported a higher rate of serositis ($p = 0.0003$), renal disorder ($p < 0.0001$) and immunologic disorder ($p = 0.04$) in males when compared with females[12]. In a similar comparative study by Hwang *et al*[14], renal disorders were found more frequently in male patients at disease onset. Serological abnormalities such as hypocomplementemia and anti-dsDNA autoantibodies are reported to be more common in male patients[12]. However, arthritis and Raynaud's phenomenon were reported to be less frequent than in females[3]. In a Latin American GLADEL's study by Garcia *et al*[6], male cohort patients showed a distinctive profile with shorter delay to diagnosis, higher incidence of constitutional symptoms, arterial hypertension, renal disease, haemolytic anaemia, IgG anticardiolipin antibodies, low C3 and higher mortality rate[6].

In comparison with studies outside Africa and Ghana (Table 2)[6,11,14,15], arthritis and cutaneous lesions were the most common manifestations across board with a low frequency of mucosal involvement (2%) and serositis (7.3%) in Hong Kong[15] and Latin America[6] cohorts respectively. But, a high frequency of serositis (61.5%) and oral manifestations (54.5%) was observed in the Ghanian series[11]. Likewise, albeit with, a low sample size, this study also found a high frequency of arthritis amongst our cohort with a low frequency of serositis and malar rash with no mucosal involvement. Severe lupus manifestations were recorded in 40% of our subjects. Renal involvement was more prevalent in Swedish (54.2%)[12] and Korean cohorts (62.3%)[14] while neurological manifestations were most frequent in Ghanaian cohort (46.2%)[11]. Haematological symptoms were more common in Asian (83%)[14] and European (60.2%)12 cohorts than in Ghanaian and our cohorts.

The average age at onset in our study was 31.2 ± 8.3 (SD) years, which was comparable to 30.62 ± 8.47 years and 31 ± 2.1 years reported by Dey *et al*[11] in Ghana and Mok *et al*[15] respectively. Ramirez *et al*[12] reported a higher mean age of 40 ± 19. Table 2 compares results from four different studies.

Male sex has been historically recognized as a bad prognostic factor for lupus. This is consistent with what was reported in the LUMINA study by Andrade *et al*[13], where accrual time and disease duration were shorter in the male patients, and higher early damage scores were independently associated with male SLE, which may account for the poorer long-term prognosis observed in male lupus patients. However, this is not in agreement with what was found by Garcia *et al*[6] where no statistical differences in sex regarding mortality was reported. In addition, no mortality was recorded in this cohort and the Ghanaian cohort[11]. The severity has been noted to be lower in males compared with females; however, the frequency of these severe flares is not significantly lower[15]. A case series of male lupus by Ambrose *et al*[16] reported sub-optimal response to standard treatments, with poor prognosis in males.

Pathogenesis of SLE is similar in both sexes; involving genetic, hormonal and environmental factors. However, studies on the differences in sex-specific genetic risk reported a significantly higher genetic risk for SLE in males than females; more specifically, the frequency of two risk alleles in the HLA locus was significantly higher in males[4]. Studies have suggested that Y-chromosome may be an important protective factor in the development of SLE in males[17]. As X-chromosome encodes several immune real immune-related as CD40 and TLR7, the presence of multiple X-chromosomes in males such as in Klinefelter's syndrome (47, XXY), is seen as a risk factor for the development of SLE in males, as well as hypogonadism from any cause[17,18].

The limitations of this study include the small number of males participants, which prevents any significant clinical inferences and report generalization. However, this study agreed with previous research in demonstrating the occurrence of multi-system lupus affectation in males, as well as females.

In conclusion, systemic lupus erythematosus though considered as women's disease, has been documented in males. Whilst clinical presentations in males are similar to those documented in females, some studies have demonstrated certain peculiar features such as delayed diagnosis, early disease accrual, higher mortality, and poorer response to standard treatment are the features

noted particularly. There is a possibility of missed diagnosis, hence a high index of suspicion is needed for early diagnosis, prompt management and reduced morbidity in males.

Acknowledgment

To Dr Ashira Blazer, Academic Rheumatologist, HSS,USA.

Funding: None was received.

Conflict of interest: None to declare.

References

1. Fortuna G, Brennan MT. Systemic lupus erythematosus: epidemiology, pathophysiology, manifestations, and management. *Dental Clinics.* 2013; **57**:631–655.
2. do Socorro Teixeira Moreira Almeida M, da Costa Arcoverde J, Barros Jacobino MN, *et al.* Male systemic lupus erythematosus, an overlooked diagnosis. *Clin Pract.* 2011; **1**: e103.
3. Yacoub Wasef SZ. Gender differences in systemic lupus erythematosus. *Gend Med.* 2004; **1**:12–17.
4. Schwartzman-Morris J, Putterman C. Gender differences in the pathogenesis and outcome of lupus and of lupus nephritis. *Clin Develop Immunol.* 2012; **2012**:604892.
5. Fairweather D, Frisancho-Kiss S, Rose NR. Sex differences in autoimmune disease from a pathological perspective. *Amer J Path.* 2008; **173**: 600–609.
6. Garcia MA, Marcos J, Marcos A, *et al.* Male systemic lupus erythematosus in a Latin-American inception cohort of 1214 patients. *Lupus.* 2005; **14**: 938–946.
7. Alonso-Perez E, Suarez-Gestal M, Calaza M, *et al.* Lack of replication of higher genetic risk load in men than in women with systemic lupus erythematosus. *Arthritis Res Therapy.* 2014; **16**:1–8.
8. Shen N, Fu Q, Deng Y, et al. Sex-specific association of X-linked Toll-like receptor 7 (TLR7) with male systemic lupus erythematosus. *Procced National Academ Scie.* 2010; **107**:15838–43.
9. Adelowo O, Oguntona S. Pattern of systemic lupus erythematosus among Nigerians. *Clin Rheumatol.* 2009; **28**:699–703.
10. Emorinken A, Dic-Ijiewere M, Erameh C, *et al.* Clinical and laboratory profile of systemic lupus erythematosus patients at a rural tertiary centre in South-South Nigeria: experience from a new rheumatology clinic. *Reumatologia/Rheumatology* 2021; **59**: 402–410.
11. Dey D, Ofori E, Hutton-Mensah KA, *et al.* Clinical characteristics of males with systemic lupus erythematosus (SLE) in an inception cohort of patients in Ghana. *Ghana Med J.* 2019; **53**: 2–7.
12. Ramírez Sepúlveda JI, Bolin K, Mofors J, *et al.* Sex differences in clinical presentation of systemic lupus erythematosus. *Biol Sex Differ.* 2019; **10**: 60.
13. Andrade RM, Alarcón GS, Fernández M, *et al.* Accelerated damage accrual among men with systemic lupus erythematosus: XLIV. Results from a multiethnic US cohort. *J Amer Coll Rheumatol.* 2007; **56**: 622–630.
14. Hwang J, Lee J, Ahn JK, *et al.* Clinical characteristics of male and female Korean patients with systemic lupus erythematosus: a comparative study. *The Korean J Intern Med.* 2015; **30**:242–249.
15. Mok C, Lau C, Chan T, *et al.* Clinical characteristics and outcome of southern Chinese males with systemic lupus erythematosus. *Lupus.* 1999; **8**:188–196.
16. Ambrose N, Kearns G, Mohammad A. Male lupus: a diagnosis often delayed—a case series and review of the literature. *Irish J Med Sci.* 2011; **180**:279–282.
17. Ortona E, Pierdominici M, Maselli A, *et al.* Sex-based differences in autoimmune diseases. *Annali dell'Istituto Superiore di Sanita.* 2016; **52**:205–212.
18. Lu L-J, Wallace DJ, Ishimori ML, *et al.* Male systemic lupus erythematosus: a review of sex disparities in this disease. *Lupus.* 2010; **19**:119–129.