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Systemic Lupus Erythematosus (SLE) & Lupus Nephritis (LN) in Male: Presentation, Outcome & Poor Prognostic Factors

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ABSTRACT

Introduction: Systemic lupus erythematosus (SLE) is common in female, while lupus nephritis (LN) is more common in male. Methods: we analyze clinical & lab parameters of male SLE patients since 2009, also reported incidence, histopathological classes & outcome of LN. Results: Total 61 male patients were diagnosed with SLE. Antinuclear antibody (ANA), Ant Ds DNA antibody (ds DNA Ab) & Lupus anticoagulant (LA) were positive in 75.40%, 67.21% & 40.98% of patients respectively, also Low C3 & C4 were observed in 57.09% & 34.70% respectively. Incidence of LN was 54.09%. Constitutional manifestations were most common presenting complain in both LN & rest of the SLE patients (RoSLE) (LN vs RoSLE: 48.48% vs 57.14% p-value: >0.05). Regarding lab parameters, RoSLE patients show more positive ANA (LN vs RoSLE: 69.69% vs 82.14%, p=>0.05), ds DNA Ab (LN vs RoSLE: 60.60% vs 75%, p=>0.05) & LA (LN vs RoSLE: 33.33% vs 50%, p=>0.05) titer. Mean creatinine (Cr) was 0.90±0.70 mg/dl in LN & 0.81±0.23 (p=>0.05) in the RoSLE patients. also decrease serum Albumin (Alb) was observed in LN patients (LN vs RoSLE: 2.85±1.85 vs 4.25±0.82, p=<0.05). Class IV was most common lesion in 48.48%, also 24.24% LN patients reached to chronic kidney disease stage V. CKD V-LN patients were older (CKD vs CKD-V: 37.68±12.18 vs 43±10.75, p=<0.05) & have positive ANA (37.5%), ds DNA ab (37.5%) & LA (25%) titer, also low C3 were more common in CKD-V patients than low C4 [CKD other stages vs CKD-V: (Low C3; 44% vs 62.5%, p>0.05) & (Low C4; 32% vs 25%, p>0.05). Median Cr & Alb was 0.9(0.52) & 2.6(1.7) in other stages of CKD, while 2.8(4.9) & 3.17(1.27) in CKD-V patients. Mean duration from diagnosis of LN to attend CKD-V was 13.34±7.50 years. Conclusion: More than half of SLE patients had LN, with class IV is most common histopathological lesion. Incidence of CKD-V in LN was significantly high, belongs to older age group and have minimal extra-renal manifestations, that probably explains late presentation & relatively poor renal outcome, however there was no statistical significant risk factor between LN & the RoSLE.

Keywords: Systemic lupus erythematous, Lupus Nephritis, Chronic Kidney disease.

INTRODUCTION

Systemic lupus erythematosus (SLE) is clinically heterogeneous, autoimmune disease with unknown etiology, characterized by autoantibodies & immune complexes affecting self-proteins, that leads to organs damage. For its high prevalence in female, it is known as women's disease. (1,2). Interaction between multiple factors e.g. genetic, environment, immunological & hormonal drives the clinical onset of SLE (3,4). The most common & earliest manifestation of SLE are constitutional, mucocutaneous & musculoskeletal, however it can affect any organ including hematologic, renal, neuropsychiatric, cardiovascular & respiratory. Different organ involvement does not manifest simultaneously and there could be time interval of months to years between different organ manifestations occur (3). Different diagnostic criteria & disease

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activity scores including the American college of Rheumatology (ACR) criteria are designed for diagnosis, monitor disease activity & research purpose, however clinical judgement is integral for diagnosis of SLE (5,6). Lupus nephritis (LN) is the term used when SLE affects kidneys, manifestation range from minimal renal involvement in the form of mild proteinuria to chronic kidney disease (CKD) stage V. Incidence of CKD-V in LN is 5-22% (7,8). The Gold standard tool for diagnosis & prognosis of LN is renal biopsy & that are reported according to International society of Nephrology (ISN) & Renal Pathology Society (RPS) guidelines (9). Idea of this study is to analyze clinical & lab parameters of SLE in male patients, also report incidence, outcome & poor prognostic factors of LN in male.

MATERIAL & METHODS

Male patients diagnosed with SLE were inducted from medical record of Dubai Hospital, Dubai, United Arab Emirates from 2009 for this retrospective observational study. Demographic features including sex, gender & clinical features were recorded. Lab parameters including blood count (Hemoglobin, leucocyte count & platelet), serum creatinine (Cr mg/dl), albumin (g/dl), urine routine, urine protein creatinine ratio (Urine PCR, g/g?), anti-lupus antibody, serum double strand deoxynucleotide antibody (anti dsDNA, IU/ml), serum antinuclear antibody (S.ANA), serum complement C3 & C4 (S.C3 & S.C4, mg/dl?) were analyzed. Anti dsDNA (titer <10 IU/ml: negative) antibody were determined by immunometric enzyme immunoassay (company?), S.ANA (<10: negative, >10: positive) by immunometric enzyme immunoassay (company?) and S.C3 & S.C4 (range?) by quantitative turbidimetric assay (company?). Renal biopsy was performed in SLE patients with proteinuria (Urine PCR >0.25 g/g) to diagnose LN. Light microscopy, immunofluorescence & electron microscopy was performed on renal tissue and changes in glomerular, blood vessel & tubule-interstitial compartment were reported according to ISN/RPS 2003 classification of LN.

Statistical Methods

Continuous variables are described as mean ± standard deviation and median with interquartile range values for normally distributed and non-normally distributed data, respectively. Categorical variables were presented as frequency and percentage. Independent t-test and Mann-Whitney test were used for normally distributed and non-normally distributed continuous variables respectively, and categorical data were compared with the help of Pearson's $\chi 2$ test or Fischer's exact test. A p-value of <0.05 was considered statistically significant. SPSS version 20 was used for statistical analysis.

RESULTS

There were 61 male patients diagnosed with systemic lupus erythematosus (SLE) since 2009 in Dubai hospital. Their mean age was 40.27±13.27 years, 54.09% were less than 40 years of age & less than 5% were above 60 years, also mean age at diagnosis was 30.43±12.93 years. 40 (65.58%) patients were Arab and 21(34.42%) were non-Arab. Constitutional symptoms (n=32, 52.45%) were most common presenting features, followed by polyarthralgia/polyarthritis (n=24, 39.34%) & skin manifestations (n=23, 37.70%), also neurological & cardiac manifestations were reported in 13.11% (n=8) & 6.55% (n=4) respectively. Regarding lab parameters, Antinuclear antibody (ANA), Ant Ds DNA antibody (ds DNA Ab) & Lupus anticoagulant were positive in 75.40% (n=46), 67.21% (n=41) & 40.98% (n=25) of patients respectively, also Low C3 & C4 were observed in 57.09% (n=33) & 34.70% (n=23) respectively. Median creatinine was 0.9(0.47) mg/dl & albumin 4.1(1.62) g/dl. Incidence of lupus nephritis

(LN) in our study population was 54.09% (n=33), we compared lupus nephritis (LN) patients (54.09%, n=33) with the rest of SLE patients (RoSLE) (44.91%, n=28). There was no statistical difference in median age & age at diagnosis between two groups [(Age in years: LN vs RoSLE: 40.76±12.26 vs 40.57± 14.71, p-value: >0.05) & (Age at diagnosis: LN vs RoSLE: 28.66±11.92 vs 32.59± 14.40, p-value: >0.05)]. Constitutional manifestations were most common presenting complain in both groups (LN vs RoSLE: 16,48.48% vs 16,57.14% p-value: >0.05), polyarthralgia/polyarthritis & skin manifestations were second most common in LN (LN vs RoSLE: 13,46.42% vs 11,33.33% p-value: >0.05) & the rest of SLE patients (LN vs RoSLE: 9, 27.27% vs 14, 50% p-value: >0.05) respectively, followed by neurological (LN vs RoSLE: 5, 15.15% vs 3, 10.71%, p=>0.05), also cardiac manifestations were more common in the rest of SLE patients than LN (LN vs RoSLE: 2, 6.06% vs 2,7.14%, p=>0.05). Regarding lab parameters, the rest of SLE patients show more positive ANA (LN vs RoSLE: 23,69.69% vs 23,82.14%, p=>0.05), ds DNA Ab (LN vs RoSLE: 20, 60.60% vs 21,75%, p=>0.05) & lupus anticoagulant (LN vs RoSLE: 11,33.33% vs 14,50%, p=>0.05) titer than LN patients. Mean creatinine was 0.90±0.70 mg/dl in LN & 0.81±0.23 (p=>0.05) in the rest of SLE patients. also decrease serum Albumin was observed in LN patients (LN vs RoSLE: 2.85±1.85 vs 4.25±0.82, p=<0.05). Renal biopsy reveals class IV in 16 (48.48%), class V in 8 (24.24%), class III in 4 (12.13%), class II in 2 (6.06%) & class I in one patient, also one patient had mix features of class III/V & IV/V each. Eight (24.24%) LN patients reached to chronic kidney disease stage V. CKD V-LN patients were older than Other CKD patients (CKD vs CKD-V: 37.68±12.18 vs 43±10.75, p=<0.05), CKD-V patients have either pedal swelling (n=6, 75%), constitutional symptoms (n=1, 12.5%) or skin manifestations (n=1, 12.5%) on presentation, while other CKD patients predominantly present with constitutional symptoms (n=15, 60%), polyarthralgia (n=11, 44%), skin manifestation (n=8,32%), also CNS manifestations were observed in 20% (n=5) & Cardiac manifestations in 8% (n=2) patients. In CKD-V patients, positive ANA, ds DNA ab & lupus anticoagulant were noticed in three (37.5%), three (37.5%) & two (25%) patients respectively, where as in other stages of CKD these antibodies were positive in 20 (80%, p=<0.05), 17(68%, p=>0.05), 9(36%, p=>0.05) patients respectively, low C3 were more common in CKD-V patients than low C4 [CKD other stages vs CKD-V: (Low C3; 11, 44% vs 5, 62.5%, p>0.05) & (Low C4; 8,32% vs 2,25%, p>0.05). Median (IQR) creatinine & albumin was 0.9(0.52) & 2.6(1.7) in other stages of CKD, while 2.8(4.9) & 3.17(1.27) in CKD-V patients. Mean duration from diagnosis of LN to attend CKD-V was 13.34±7.50 years.

DISCUSSION

Association of estrogen with autoimmune disease is hypothesized for high incidence of SLE in female. T-cell dysregulation and hyperactivity of B cells as well as helper T cells generate autoantibodies (10-15). Strong association between TLR7 & SLE in eastern Asian male than female was found by Shen et al (16). Androgen hormone in male are responsible for renal injury in SLE patients (17).

In this study, we collected data on clinical & immunological features of SLE in 61 male patients in the period of 24 years (1998 to 2022). Mean age at diagnosis was 30.43±12.93 years, which is more than reported previously in Dubai population by Alsaleh et al (28.9 years in male & female patients) (18), Arab World (Marwan, 28.9 years in male & female) (19), Europeans (20) & Latin Americans (2) (29 and 28 years, respectively). Common presenting features were constitutional manifestation & arthralgia/arthritis, same observation was observed in other Arab patients (19) & European patients (20). Neuropsychiatric manifestations were observed

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in 13.11% patients in our study population, while it was reported in 15.6% SLE patients in Dubai (AlSaleh, 28.9 years, male & female) (18), 30% & 27% in patients from Arab data (19) and European (20) patients respectively, also Cardiac manifestation were quite commonly reported in Latin American patients (42.9%)(21), reported in 14.4% of patients from Arab countries (19) , while only 6.55% patients had this manifestation in our study population. Venous thrombosis manifest in 14% of European patients (20), while 9.8% in our population & 8.3% in patients from different Arabic countries (19). Positivity rate for ANA in SLE patients from Europe (20), Latin America (21) & Arab countries (overall) (19) was more than 95%, whereas 77.75% &75.4% patients from Saudi Arab (22) & our study population respectively had ANA positive. In our male SLE study population, Anti-dsDNA was positive in 67.21% patients, that is less than reported in European (20) & Latin American (21) SLE patients (78% & 70.5% respectively), however in Arab world it ranges from 46.5% in Kuwait (23) to 91.8% in Oman (24). Complement consumption is observed is as much as 57.09% male SLE patients, however C3 is consumed more in our population than C4 (Low C3 57.09% & Low C4 34.70%), while in Latin American (21) patients C4 consumption is more (Low C3 49.3% & Low C4 53.80%) and both are almost equally consumed is in general SLE patients from different Arab countries (Low C3 53.70% & Low C4 52.40%) (19). Lupus anticoagulant is positive in 40.98% of our male SLE patients, which is consistent with Arab SLE patients (42%) (19), whereas low positivity rate is reported in European (20) & Latin American (21) SLE patients (15% & 30% respectively). Renal disease in SLE carries significant risk of morbidity & mortality, it develops in 25-75% SLE patients (25,26) and 5-22% of these patient progress to end stage kidney disease requiring dialysis or transplantation (27,28). Studies have shown that LN is more common in male than female (29) Genetic, sex hormones & autoimmunity is implicated factors. We observed lupus nephritis (LN) in 54.09% in our male SLE patients, which is consistent with observation from Latin American (21) & Arab SLE patients (51.7% & 50.4% respectively) (19), however incidence of LN was lower in European SLE patients (39%) (20), also Basu et al & de Carvalho et al reported incidence of LN in male as low as 9.67 & 13.6% respectively (30,31). The mean age at diagnosis for our LN patients was 28.6±11.92 years, which is lower than reported by Wang et al (32.67±13.96 years) (32). Patel et al observed increase in LN prevalence in male with increase in age (33) and we did not observe statistical age difference at diagnosis between LN & the rest of SLE. In our Male LN patients, the most common manifestation was pedal edema 21(63.63) (hematuria?). Constitutional manifestation e.g. fever, arthralgia & body aches was common in our patients (48.48%, n=16), while Patel et al (33) observe these in only in 27.58% LN male patients. Medina et al (34), de carvalho et al (31) & Liu et al (35) reported higher incidence of skin rash in male LN patients (84%, 45.5% &49.4% respectively) whereas only 9(27.27%) male LN patients had skin rash in our study. Hopkin et al (36) & GLADEL (37) found neuropsychiatric & cardiac manifestations common while Molina et al (38) & Stefanidou et al (39) reported vascular thrombosis commonly in male SLE patients, for our patients' neuropsychiatric symptoms (15.15%), venous thrombosis & cardiac manifestation (6.06% each) were uncommon. Mean Proteinuria in male LN patients was 2.21±5.22 gm/day and only four patients (12.12%) had nephrotic range proteinuria, which is associated with class V in two patients & class III & IV for one patient each which is consistent with observation reported by Patel et al (33) & Liu et al (35). Wang et al (32), also Hsu et al (40) reported urinary protein excretion of high magnitude (5.26 & 5 gm/day). In male LN patients, high anti ds DNA titer is reported in 60-100% (32,33) of patients & high ANA titer is observed in 74-98% (32,41) of patients, however high anti ds DNA & ANA titer was observed in 60.60% & 69.69% in our study patients. The median serum creatinine in our population was 0.9 mg/dl (0.4-22 mg/dl), class

IV & class V is associated with creatinine > 1.2 mg/dl in 43.75% (n=7) & 37.5% (n=3) male LN patients respectively. Patel et al (33) reported 70% of class IV male LN patients had creatinine >1.4 mg/dl, while class II & III were associated with mean creatinine <1.4 mg/dl. Urrestarazú et al (41) & Carvalho et al (31) observed high mean serum creatinine in their population (2.18±1.47 & 3.16±2.49 mg/dl respectively). Class IV was most common histology lesion in our study population (48.48%, n=16), Wang et al (60%) (32) & liu et al (35.7%) (35) also reported class IV as most common lesion in their study population, however de Carvalho (31) reported class V lesion in 45.5% of patients and this lesion is observed in 24.24% patients in our study. We found low albumin only statistically significant factor between lupus nephritis & the rest of SLE patients. Eight LN patients (24.24%) progress to CKD stage V and ultimately require renal replacement therapy, CKD V patients belong to older age group and have minimal extra-renal manifestations, that probably explains late presentation & relatively poor renal outcome. Class IV lesion is predominantly associated with CKD-V (50%), Neither autoimmune antibody titer nor low complement levels is associated with progression to CKD-V. Despite decreasing trend over last decade, still incidence of ESKD in lupus nephritis is 20% (42,43). Tektonidou et al (43) reported highest risk of ESKD was associated with Class IV, with 5 years, 10 year & 15 years risk of 19%,33% & 44% respectively in studies from developed countries between 2000-2006, also risk of ESKD was low with class V (4%,11% & 20% for 5, 10- & 15-year risk respectively). Ethnicity, younger age, male sex, diffuse proliferative glomerulonephritis, deranged renal functions on diagnosis, nephrotic range proteinuria, hypertension & diabetes are known poor prognostic factors regarding progression of LN to CKD-V (44), also Tselios et al reported poor compliance, histopathological features like collapsing GN, thrombotic microangiopathy & concomitant anti GBM nephropathy are associated with poor renal outcome (45).

CONCLUSION

SLE affects male but incidence is low, however more than half of patients had LN, also incidence of CKS-V in LN was significantly high, most common histopathological lesion was class IV. There was no statistically significant risk factor between LN & the rest of SLE patients. Among LN patients CKD V patients belong to older age group and have minimal extra-renal manifestations, that probably explains late presentation & relatively poor renal outcome.

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Table 1

Demographic chrarcterstics	Total Patients	Lupus Nephritis (n=33,54.09%)	Rest of SLE (n=28, 44.91%)	p-value
Age in Years, Mean (STD)	40.27(13.27)	40.76(12.26)	40.57(14.71)	0.870457
<40 years	33(54.09)	18(54.54)	15(53.57)	
40-60 years	25(40.98)	15(45.45)	10(35.71)	
>60 years	3(4.91)	0(0.00)	3(10.71)	
Age at diagnosis in Years, Mean (STD)	30.43(12.93)	28.66(11.92)	32.59(14.40)	0.292827
Nationality				
UAE	33(54.09)	20(60.60)	13(46.42	
India	8(13.11)	1(3.03)	7(25)	
Pakistan	5(8.19)	1(3.03)	4(14.28)	
Nepal	3(4.91)	2(6.06)	1(3.57)	
Philipine	2(3.27)	1(3.03)	1(3.57)	
Egypt	2(3.27)	0(0.00)	2(7.14)	
Yemen	2(3.27)	1(3.03)	1(3.57)	
Bahrain	1(1.63)	0(0.00)	1(3.57)	
Cameron	1(1.63)	1(3.03)	0(0.00)	
KSA	1(1.63)	0(0.00)	1(3.57)	
Sudan	1(1.63)	1(3.03)	0(0.00)	
Tanzania	1(1.63)	1(3.03)	0(0.00)	
UK	1(1.63)	1(3.03)	0(0.00)	
Organ involvement				
CNS Manifestation	8(13.11)	5(15.15)	3(10.71)	0.608932
Cardiac Manifestation	4(6.55)	2(6.06)	2(7.14)	0.864883
Skin Manifestation	23(37.70)	9(27.27)	14(50)	0.067982
Constitutional Manifestation	32(52.45)	16(48.48)	16(57.14)	0.499833
Arthralgia	24(39.34)	11(33.33)	13(46.42)	0.296811
Hematological Manifestation	29(47.54)	15(45.45)	14(50)	0.723155
DVT	6(9.83)	2(7.14)	4(12.12)	0.2824
Pedal edema	24(39.34)	21(63.63)	3(10.71)	
Creatinine mg/dl. Median (IQR)	0.9(0.47)	0.9(0.7)	0.81(0.23)	0.087838
Lupus nephritis	33(54.09)	33(54.09)		
Class V	5(15.15)	8(24.24)		
Class IV	11(33.33)	16(48.48)		
Class II	2(6.06)	2(6.06)		
Class III	1(3.03)	4(12.12)		
Class I	1(3.03)	1(3.03)		
Class IV/V	1(3.03)	1(3.03)		
Class III/V	1(3.03)	1(3.03)		
Lupus Anticoagulant				
positive	25(40.98)	11(33.33)	14(50%)	0.187186
Anti ds DNA	N=61			
positive	41(67.21)	20(60.60)	21(75)	0.232726
C3				

Low	33(54.09)	16(48.48)	17(60.71)	0.339502
C4				
Low	23(37.70)	10(30.30)	13(46.42)	0.195331
ANA				
positive	46(75.40)	23(69.69)	23(82.14)	0.260644
Urine routine				
NA	16(26.22)	9(30)	7	
Protein	12(19.67)	10(33.33)	2	
Active sediment	3(4.91)	3(10)	0	
Blend	5(8.19)	0(0.00)	5	
RBC >5	9(14.75)	7(23.33)	2	
Alb Median (IQR)	4.1(1.62)	2.85(1.85)	4.25(0.82)	0.000353
<3.5 g/dl	14(22.95)	9(30)	5	
≥ 3.5 g/dl	47(77.04)	8(26.66)	12	
NA	27(44.26)	13(43.33)	14	

Table 2: comparison of CKD-V & other stages of CKD

	CKD (n=25,75.76%)	**ESKD (n=8,24.24%)**	**P-value**
Age in Years, Mean±STD	37.68±12.18	43±10.75	0.028565
Age at diagnosis in Years, Mean±STD	28.84±11.49	28.5±19	0.937889
Nationality			
UAE			
CNS Manifestation	5(20)	0(0.00)	0.169686
Cardiac Manifestation	2(8)	0(0.00)	0.409143
Skin Manifestation	8(32)	1(12.5)	0.281077
Constitutional Manifestation	15(60)	1(12.5)	0.019293
Arthralgia	11(44)	0(0.00)	0.021572
Hematological Manifestation	13(52)	2(25)	0.181904
Pedal edema	11(44)	6(75)	0.126752
Thrombosis	2(8)	0	
Creatinine mg/dl.Median(IQR)	0.9(0.52)	2.8(4.9)	0.186797
Lupus nephritis			
Class IV	16(48.48)	0(0.00)	0.169686
Class V	8(24.24)	4(50)	0.250592
Class III	4(12.12)	0(0.00)	0.409143
Class II	2(6.06)	0(0.00)	0.565659
Class I	1(3.03)	0(0.00)	0.565659
Class IV/V	1(3.03)	0(0.00)	0.565659
Class III/V	1(3.03)	1(12.5)	0.072626
ANA			
positive	20(80)	3(37.5)	0.022807
Lupus Anticoagulant			
positive	9(36)	2(25)	0.565659
Anti ds DNA			
positive	17(68)	3(37.5)	0.12437
C3			
Low	11(44)	5(62.5)	0.36214
C4			

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Low	8(32)	2(25)	0.707677
ANA			
positive	20(80)	3(37.5)	0.022807
Urine routine			
Protein	17(68)	3(37.5)	
Blend			
RBC >5	10(41.66)	3(37.5)	
PCR	3.15(3.42)		
Alb Median (IQR)	2.60(1.70)	3.17(1.27)	0.853648
<3.5 g/dl	9(36)	3(37.5)	
≥ 3.5 g/dl	16(64)	5(62.5)	