ORIGINAL ARTICLE

Clinical presentation of Systemic Lupus Erythematosus in a Rheumatology Centre in Malaysia.

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Abstract

Introduction: Systemic lupus erythematosus (SLE) is a complex autoimmune disorder with a wide spectrum of clinical phenotypes. SLE is a common diagnosis in daily clinical practice with or without cutaneous manifestations. We performed a retrospective study on lupus to delineate the differences between SLE and cutaneous lupus based on the American College of Rheumatology classification criteria for SLE.
Method: Records for all patients' who were diagnosed with lupus erythematosus were retrieved from the rheumatology clinic. The basic clinical and demographic information were reviewed and analyzed.
Results: There were 330 patients of whom females formed the majority (93.6%), with a mean age of 43.3 ± 14.5 years and the mean age at diagnosis was 34.5 years. Ethnic stratification revealed that Malays formed the highest proportion (n=165, 50%) followed by Chinese (n=123, 37.3%) and Indians (n=33, 10%). Mean duration of disease was 8.9 ± 7.6 years and 293(88.9%) patients had the disease for more than 2 years. Overall, malar rash (n=109, 33.0%), oral ulcer (n=99, 30.0%), and photosensitive rash (n=91, 27.7%) were the common cutaneous lesions at baseline. ANA, anti-dsDNA, and anti-Sm antibodies were positive in 242 (73.3%), 111(33.6%) and 23(7.0%) of patients respectively. 67.3% of patients with positive ANA and without mucocutaneous manifestations, presented with at least one system involvement.
Conclusion: Definitive diagnosis of SLE in our cohort is challenging as this was a retrospective study and we had to confine ourselves to the data in the patient records. This study provides useful information on the common manifestations of SLE in this single centre.
Keywords: Cutaneous lupus erythematosus, Systemic lupus erythematosus, American College of Rheumatology Criteria, clinical manifestations.

Introduction

Lupus erythematosus (LE) is a complex autoimmune disease characterized by a wide spectrum of clinical manifestations. The underlying etiology and pathogenesis remains obscure. Genetic, and environmental factors have been implicated in the development of this incurable condition.[1,2] Systemic lupus erythematosus may present with cutaneous lupus as a clinical progression predictor. [3, 4, 5] Malar rash, discoid rash, photosensitive rash and oral ulcers are well recognized with a high sensitivity and specificity, and thus, included as four separate entities in the 1997 Revised American College of Rheumatology (ACR) Criteria for SLE. [6] Other skin manifestations may be non-specific, being found in other autoimmune conditions as well as in LE. A wide spectrum of cutaneous lesions has been included in The Systemic Lupus International Collaborative Clinics (SLICC) criteria.[7] SLE may be difficult to diagnose despite a positive ANA with either a barely positive or negative anti-dsDNA antibody. ANA and anti-dsDNA are present in > 95% and 70% of SLE patients respectively.[8] When the diagnosis is in doubt, close follow up and surveillance is needed and treatment should not be delayed. Obviously patient with lupus nephritis (LN), will be labelled as SLE with or without other clinical, immunological or serological features as per ACR criteria.

Materials and methods

This is a hospital-based case series analysis conducted at the single tertiary referral rheumatology center Hospital Raja Permaisuri Bainun (HRPB), Ipoh, Perak state of Malaysia in 2018-2019. All the patients who were diagnosed as lupus erythematosus (either SLE according to 1997 Revised ACR criteria for SLE or other non-specific cutaneous lesions related to lupus which are not part of ACR domain) from the rheumatology clinic were included. Patients' detailed information at baseline such as the demographic characteristics, duration of disease, clinical manifestations, laboratory investigations, and treatment were retrieved from the clinical records.

Definite diagnosis of SLE was based on the presence of 4 out of 11 of ACR criteria. However, SLE was also diagnosed if patient had histologically proven lupus nephritis even without other clinical domain according to the ACR criteria. A probable diagnosis of SLE with high index of suspicion was made, when the clinical features did not fulfill ACR criteria i.e., less than four as recommended without positive serological and immunological markers.

Immunological markers such as anti-nuclear antibody (ANA), anti-double stranded deoxyribonucleic acid antibody (anti-dsDNA), and anti-Smith antibody (anti-Sm) were recorded qualitatively according to our laboratory setting. Anti-dsDNA was only tested if the ANA result was in homogenous pattern. Hence, the ANA may be recorded as positive but anti-dsDNA were considered negative if it was not available or documented. Other antibodies such anti-cardiolipin (aCL), lupus anti-coagulant (LAC), extractable nuclear antigens (ENA) tests were performed with strict indications and justifications.

Ethics

The institutional ethics committee approved the study design and registered in the National Medical Research Registry (NMRR-19-177-45651).

Statistical analysis

Statistical analysis was performed using SPSS version 23 (Institutional licensed). Descriptive statistics was done using frequency distribution tables. Non-parametric statistical tests performed to study the difference in continuous dependent variables between categories of independent variables. Association between categorical

variables were analyzed using Chi-square test. Level of significance was fixed at 0.05.

Results

Out of a total of 330 patients, females outnumbered males (n=309, 93.6% vs. n= 21, 6.4%). Malay was the predominant ethnic group (n=165, 50%) followed by Chinese (n=123, 37.3%), and Indian (n=33, 10.0%) (P=0.010) with an overall mean age of 43.3 years and the age at diagnosis of lupus was 34.5 years. The majority of patients were between 20 – 60 years. The mean duration of disease from the year of diagnosis till the point of collection of data for this research was 8.9 years while most patients had the disease for more than 2 years (Table 1).

A significantly higher proportion of patients fulfilled more than 4 of the ACR criteria as recommended (P = 0.001). The median (IQR) ACR criteria domain fulfilled was 4 (0 – 8). Arthritis was the commonest presentation (n=215, 65.7%) followed by hematological domain (AIHA, cytopenia) (n=122, 37%), malar rash (n=109, 33%), mucocutaneous ulcer (n=99, 30%), and photosensitive rash (n=91, 27.7%). Discoid lupus which is also classified as chronic cutaneous lupus, was observed in 53 (16.2%) of the patients. Among LE specific cutaneous lesions, alopecia was one of the commonest presentation observed (n=157, 47.6%). Alopecia, malar rash, mucocutaneous ulcer and photosensitive rash were frequently observed in patients with a positive ANA. However, only 40% of these features were seen in patients with a positive anti-dsDNA antibody.

The ANA and anti-dsDNA antibodies were detected in more than 73% and 34% of patients respectively at baseline. Anti-Sm antibody was observed in 7.3% of patients. Other autoantibodies such as anti-cardiolipin and lupus anti-coagulant were detected in a few patients who presented with mainly neurological manifestations such cerebrovascular accident (CVA) and seizures. Anti-Ro, anti-La and anti-RNP antibodies were tested in patients who were suspected to have overlap syndrome or mixed connective tissue disease.

ANA, anti-dsDNA and anti-Sm antibodies were present very significantly in patients with SLE who fulfilled ≥ 4 out of 11 ACR criteria over those who fulfilled < 4 criteria (156 (90.2%), 85(49.1%) and 20(11.6%) vs 86(54.6%), 26(16.6%) and 3(1.9%) respectively). (p=0.001). ANA was detected in females more than in male patients (p=0.019). Anti dsDNA antibodies was also detected more frequently in female patients but did not reach statistical significance. Hypocomplementemia (C3 and C4) was significantly detected in patients with positive ANA and anti-dsDNA antibody (C3, n=90, 37.2%; n=47, 42.3% and C4, n=71, 29.3%, n=39, 35.1% respectively) (p = 0.0001). SLE was diagnosed in lupus nephritis from histological evidence with or without cutaneous lupus or other systemic involvement in 56 patients.

Comorbidities (DM, hypertension, IHD, dyslipidemia) were highest among patients above 40 years of age. DM, hypertension, and dyslipidemia (p=0.007) were common among Malay female patients (p = 0.001), and hypertension and IHD among Chinese (p = 0.004 and p=0.002 respectively).

Corticosteroids and hydroxychloroquine were commonly prescribed in the majority of patients (n=260, 78.8%; n=245, 74.2%, respectively) followed by other conventional disease modifying anti-rheumatic drugs (DMARDs) and immuno-modulators. Biologic DMARDs, however, was rarely used due to cost constraints.

Discussion

SLE is a complex autoimmune disease of unknown etiopathogenesis with spectrum of clinical phenotypes. It is a multisystem disease due the antibody-antigen complex deposition

which eventually leads to irreversible damage if treatment is delayed. Cutaneous lesions are a very common presenting feature of LE even in the absence of systemic or organ involvement and the incidence and prevalence is higher than SLE itself. [9] During the course of SLE, cutaneous lesions develop in 70% - 80% with malar rash found in 30% of patients which is consistent with our result.[10] However, the cutaneous lesions, in our study was lower.

SLE appeared to be similar between females and males in our study but other studies have shown that the presentation can be more heterogenous and also more severe in male SLE.[11, 12, 13] The occurrence of cutaneous lesions was higher in women than men in our study, consistent with other studies.[14, 15, 16] Chronic discoid lupus (DLE) was found to be more prevalent in Asians compared to Caucasians with female predominance. In this study, the female/male ratio, 5.4:1, is comparable with previous studies despite our smaller number of patients. [17,18]

Males had more severe disease in other studies especially renal involvement. [19] Systemic involvement was also significantly higher in female patient in this study similar to other previous studies. [12, 20] Non erosive arthritis and hematological involvement were a common presentation in female SLE in our cohort, similar to the findings by Tan et al. and LUMINA group.[11,21] However, even though musculoskeletal features were frequently observed in our cohort, it was much less in all patient with SLE in general.[22] Neurological manifestations and serositis were substantially higher in females although the numbers were small. The latter especially with pleuropulmonary involvement was not common in our patients compared to a previous report. [23]

The ANA, anti-dsDNA antibodies and low complements were more frequently detected in female patients in contrast with previous studies [21, 24] where the markers were higher in male SLE. The immunological markers were only measured qualitatively, e.g., ANA may be positive but depending on the immunological pattern, anti-dsDNA as a second level testing will not be measured if the ANA is not a homogenous pattern. This method of assessment is in accordance with several published international guidelines.[25, 26]

Notably, in our cohort, patients with either LE specific cutaneous lesions or non-LE specific lesions, accompanied by a positive ANA (with or without presence of other antibodies) had fulfilled the ACR criteria despite the absence of significant systemic involvement. The exception to this rule was in patients with Lupus Nephritis where the diagnosis of SLE at first presentation was based on the renal biopsy evidence alone. A few LN patients presented with cutaneous lesions of ACR domains without other systemic involvement. The ANA with antibody subtypes i.e., dsDNA was found in small number of LN. In patients with a positive anti-dsDNA, LN is a frequent finding.[27] Majority of patients with lupus nephritis are treated by the nephrologist in our hospital, hence the small number seen in our cohort of patients seen at the Rheumatology Clinic.

Our study has several limitations, most important of which was incomplete documentation in the case records. Most of the immunological markers were provided qualitatively which may lead to data discrepancy and bias. All patients were only from the rheumatology clinic. SLE patients on treatment at nephrology, dermatology and hematology clinics were not included in this study.

Conclusion

This study revealed that the majority of patients diagnosed SLE based on cutaneous lupus with positive ANA at baseline fulfilled the ACR criteria. Cutaneous lesions, arthritis and hematological manifestations were common in female SLE similar to previous studies. More prospective studies are needed to predict the

severity and progression of SLE in our multi-ethnic population with a heterogeneous genetic and environmental background. Quantitative measurement of certain biochemical, immunological and serological markers may be useful in future studies.

Conflict of Interest

The authors declare no conflict of interest.

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Table 1. Basic demographic characteristic based on the ACR classification criteria for SLE.

Clinical characteristics	Overall n (%)	≥ 4 criteria per ACR n=173	≤ 4 criteria per ACR n=157	*P*
Mean age ± SD, years.	43.3 ± 14.5	40.2 ± 13.9	46.7 ± 14.4	0.001
Mean age at diagnosis ± SD, years.	34.5 ± 13.9	32.2 ± 13.6	37.0 ± 13.8	
Gender, n (%)				
Female	309 (93.6)	163(94.2)	146(93.0)	0.002
Male	21(6.4)			
Ethnic group, n (%)				
Malay	165(50.0)	95 (54.9)	70(44.6)	
Chinese	123(37.3)	58 (33.5)	65(41.4)	0.010
Indian	33(10.0)	12 (6.9)	21(13.4)	
Others	9(2.7)	8 (4.6)	1(0.6)	
Mean Duration of disease ± SD, years.	8.9 ± 7.6	8.1 ± 6.8	9.9 ± 8.3	0.032
Duration of disease: n (%)				
< 2 years	33(10.0)	18 (10.4)	15 (9.8)	ns
> 2 years	293(68.8)	155 (89.6)	138 (90.2)	ns

Abbreviation: ACR, American College of Rheumatology; SLE, Systemic Lupus Erythematosus.

Table 2. Clinical and Immunological features according to ACR Criteria for SLE domain at baseline.

Clinical features	Overall n (%)	SLE (≥ 4 criteria per ACR) n=173	SLE (≤ 4 criteria per ACR) n=157	*P*
ACR criteria:				
Neurologic	32 (9.7)	20 (11.7)	12 (7.6)	ns
Malar rash	109(33.0)	91(52.6)	18(11.5)	0.001
Photosensitive rash	91 (27.7)	72(41.6)	19(12.1)	0.001
Discoid rash	53 (16.2)	39(22.5)	14(8.9)	0.001
Oral ulcer	99 (30.0)	77(44.5)	22(14.0)	0.001
Non-erosive arthritis	215 (65.7)	134(77.5)	81(51.6)	0.001
Serositis	21 (6.4)	17(10.0)	4(2.5)	ns
Renal	66 (20.0))	34(19.7)	32(20.4)	ns
Hematologic	122 (37.0)	89(51.4)	33(21.0)	0.001
Other cutaneous:				
Alopecia	157(47.6)	96(55.5)	61(38.9)	ns
Livedo reticularis	3(0.9)	3(1.7)	0	ns
Other features:				
Myositis	22(6.7)	15(8.7)	7(4.5)	ns
ILD	3(0.9)	3(0.9)	0	ns
Pulmonary hemorrhage	4(1.2)	2(1.2)	2(1.3)	ns
Positive Immunology tests at baseline:				
ANA	242(73.3)	156(90.2)	86(54.8)	0.001
Anti-dsDNA	111(33.6)	85(49.1)	26(16.6)	0.001
Anti-Sm	23(7.0)	20(11.6)	3(1.9)	0.001
LAC	9 (2.7)	4(2.3)	5(3.2)	ns
ACL	9 (2.7)	6(3.5)	3(1.9)	ns
Anti-Ro	56 (17)	37(21.4)	19(12.1)	0.025
Anti-La	30 (9.1)	19(11.0)	11(7.0)	ns
Anti-RNP	30 (9.1)	24(13.9)	6(3.8)	0.001
Low C3	103 (31.3)	70(40.5)	33(21.2)	0.001
Low C4	80 (24.3)	55(31.8)	25(16.0)	0.001

Abbreviation. SLE, Systemic Lupus Erythematosus; ANA, anti-nuclear antibody; dsDNA, anti-double stranded deoxyribonucleic acid antibody; anti-Sm, anti-Smith antibody; ACL, anti-cardiolipin antibody; LAC, lupus anti-coagulant; anti-RNP, anti-ribonucleoprotein; ILD, interstitial lung disease; ACR, American College of Rheumatology; ns, not significant.

Table 3. Relationship between the patient gender and age group with systemic involvement according to ACR criteria. (n=330)

	Fulfilled ACR Criteria	≥ 4 criteria	≤ 4 criteria	With systemic involvement	Positive ANA	Positive Anti-dsDNA ab
Age group: n(%)	7 (2.1)	5 (2.9)	3 (1.9)	7 (2.1)	7 (2.9)	5 (4.5)
1- 19	58 (17.6)	40 (23.1)	20 (12.7)	46 (13.9)	46 (19)	27 (24.3)
20 - 29	77 (23.3)	46 (26.6)	32 (20.4)	57 (17.7)	65 (26.9)	25 (22.5)
30 - 39	66	40 (23.1)	29 (18.5)	47 (14.2)	52 (21.5)	22 (19.8)
40 - 49	(20.00	26 (15.0)	36 (22.9)	36 (11.2)	39 (16.1)	14 (12.6)
50 - 59	60 (18.2)	12 (6.9)	29 (18.5)	21 (6.4)	25 (10.3)	13 (11.7)
60 - 69	40 (12.1)	4 (2.3)	8 (5.1)	7 (2.1)	8 (3.3)	5 (4.5)
>70	12 (3.6)					
Gender: n(%)						
Female	299	163	146	205 (62.1)	222	104
Male	(90.6)	(94.2)	(93.0)	17 (5.2)	(91.7)	(93.7)
	21 (6.4)	10 (5.8)	11 (7.0)		20 (8.3)	7 (6.3)

Table 4. Overall treatment and comorbid

	n (%)
Treatment	
Corticosteroid	260 (78.8)
Hydroxychloroquine	245 (74.2)
Azathioprine	53 (16.1)
Methotrexate	9 (2.7)
Salazopyrine	5 (1.5)
Cyclosporin	4 (1.2)
Cyclophosphamide	23 (7.0)
Mycophenolate mofetil	9 (2.7)
Calcium supplement	150 (45.5)
Vit D	114 (34.5)
Comorbid	
Hypertension	91 (27.5)
Diabetes mellitus	21 (6.4)
Ischemic heart disease	12 (3.6)
Dyslipidemia	24 (7.3)
Cancer	4 (1.2)

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