Clinical Profile and Outcomes of Filipino Lupus Patients with Myocarditis in a Tertiary Hospital

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Abstract

Introduction: Myocarditis is a rare but serious complication of systemic lupus erythematosus (SLE). Existing literature on adult Filipino SLE patients with myocarditis is limited. This study aims to determine clinical characteristics and outcomes of myocarditis in Filipino patients with lupus.

Methods: Review of medical records (between 2015 and 2017) of eight adult patients with lupus myocarditis in a tertiary government hospital was done. Clinical features, electrographic and echocardiographic findings, management, and outcomes were described.

Results: All patients were females with a mean lupus duration of 10 months at the time myocarditis was diagnosed. Half of them had severe lupus activity, mostly with concomitant hematologic activity (100%) and nephritis (75%). Echocardiography showed wall motion abnormalities in all patients, with 63% having global hypokinesia and 75% having moderate to severe hypokinesia of the left ventricular wall. Treatment included methylprednisolone pulse therapy (88%) and high-dose steroids (13%). One patient died from cardiogenic and septic shock prior to receiving MPPT. Most patients (75%) were clinically improved at the time of discharge.

Conclusion: Filipino patients with lupus typically present with myocarditis early in the course of the disease, with high disease activity and concomitant hematologic activity and nephritis. Outcomes are generally favorable with early immunosuppressive therapy.

Keywords: systemic lupus erythematosus, lupus, myocarditis, filipino

Introduction

Myocardial involvement is seen in eight to 81% of cases of systemic lupus erythematosus (SLE), with a mean prevalence of 50% internationally and 30-86% locally.[1-4] Clinically apparent lupus myocarditis, however, is rare at nine percent.[5,6] For the diagnosis of lupus myocarditis, endomyocardial biopsy is the gold standard, with exclusion of all other causes. However, due to the low specificity and perceived risks of biopsy,[7] two-dimensional echocardiography has been used instead in recent studies.[7-9] In an unpublished report by O. M. Samar-Sy et al in 1993, it was described that the most common cardiac abnormality by echocardiography was myocardial involvement, with hypertension and high steroid doses being significantly associated with cardiac abnormalities such as left ventricular (LV) systolic dysfunction and dilatation. LV dilatation was the most frequent chamber abnormality, while a small proportion (6%) had LV wall motion abnormality. In electrocardiography (ECG), features are less specific, with sinus tachycardia and non-specific ST segment and T-wave changes being the two most common findings.

There are no published studies on the clinical profile of adult Filipino lupus patients with myocarditis to date. These can guide local clinicians in the prompt diagnosis and management of this condition to avoid its acute and chronic complications. The objective of this study, therefore, is to determine clinical characteristics and outcomes of myocarditis in Filipino patients with lupus. We also aim to describe electrocardiographic and echocardiographic findings of lupus myocarditis.

Methods

This is a single-center, retrospective study of medical records of patients admitted to a tertiary government hospital (University of the Philippines Manila – Philippine General Hospital) between January 1, 2015 and December 31, 2017. All patients aged 19 years and older fulfilling the 1982 American College of Rheumatology (ACR) criteria or the 2012 Systemic Lupus International Collaborating Clinics

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(SLICC) criteria for SLE (see Appendices A and B) and having clinical lupus myocarditis were included. Lupus myocarditis was defined in this study as cardiovascular symptoms with echocardiographic wall motion abnormalities with or without decreased EF; positive biomarkers of cardiac injury; and/or electrocardiogram (ECG) findings suggestive of cardiac injury that are not attributable to other conditions.[10] Clinical findings included symptoms of exertional dyspnea, orthopnea, paroxysmal nocturnal dyspnea, chest pain, and/or palpitations; and signs such as increased heart rate, lung crackles, jugular venous distension, peripheral edema, S3 or S4 heart sounds, and/or heart murmurs. SLE patients meeting the above criteria, but whose laboratory results were incomplete and for whom myocardial biopsy was not done, were included.

Excluded were patients who had any of the following diseases or conditions that may mimic, alter, or obscure the echo findings in lupus myocarditis: 1) angiographically-confirmed significant epicardial coronary artery disease; 2) moderate to severe valvular lesions, such as stenosis or regurgitation; 3) congenital heart disease; 4) history of coronary artery bypass graft (CABG) or valve surgery prior to the diagnosis of lupus myocarditis; 5) history of rheumatic fever or infective endocarditis; 6) advanced chronic kidney diseases from causes other than lupus nephritis; 7) constrictive or restrictive myopathies proven to be of tuberculous etiology; 8) drug use (cocaine, amphetamines, anthracyclines, trastuzumab, alkylating agents, etc.); and 9) patients with cardiac devices (e.g., pacemakers and defibrillators). The study was conducted only with approval from the institutional review board.

Data extracted were analyzed according to demographic and clinical data, available imaging findings, electrocardiographic and echocardiographic findings on presentation, and in-hospital outcomes. Descriptive statistics using means and proportions were used to describe population characteristics and outcomes.

Results

Patient characteristics

Our initial search identified 16 patients with a diagnosis of lupus myocarditis, retrieved from the patient census of the Division of Rheumatology of the Philippine General Hospital. Eight patients were excluded due to a concomitant diagnosis of tuberculosis (n = 3); echocardiographic findings not consistent with myocarditis (n = 4); and the absence of a formal diagnosis of SLE (n = 1). The eight patients included were all females diagnosed with SLE between the ages 22 and 42. Table I summarizes the characteristics of this population. Patients were diagnosed with lupus myocarditis within an average of 10 months of their lupus diagnosis. Half of the patients had a severe lupus flare based on a SELENA-SLEDAI (The Safety of Estrogens in Lupus National Assessment - Systemic Lupus Erythematosus Disease Activity Index) of >12 (see Appendix C). Five out of eight patients (62.50%) were on high-dose steroids (defined as >30 but ≤100 mg/day of prednisone equivalent)[11] at the time of diagnosis of myocarditis. Hematologic activity and nephritis were common in patients with myocarditis. Dyslipidemia was found in three out of four patients, while smoking was the most common cardiovascular risk factor. All except one patient (87.50%) received methylprednisolone pulse therapy (MPPT), which was given between one and 10 days after the diagnosis of myocarditis. MPPT was administered more than 24 hours after the diagnosis of myocarditis in five out of seven patients (71.43%).

Table I. Demographics and clinical characteristics at the time of diagnosis of myocarditis (n = 8)

Variables	Mean±SD
Age in years	32.75±7.46
Disease duration in months	10.25±15.82
SELENA-SLEDAI in mean ± SD	13.38±7.03
Dose of corticosteroid at diagnosis in milligrams	116.88±71.41
Variables	n (%)
Sex	
Male	0 (0.00)
Female	8 (100.00)
Lupus manifestations	
Mucocutaneous	5 (62.50)
Arthralgia/arthritis	1 (12.50)
Serositis	3 (37.50)
Nephritis	6 (75.00)
Hematologic	8 (100.00)
Nervous system involvement	0 (0.00)
Vasculitis	0 (0.00)
Co-morbidities	
Antiphospholipid syndrome	1 (12.50)
Hypertension	1 (12.50)
Diabetes mellitus	0 (0.00)
Dyslipidemia	4 (75.00)*
Recent viral infection or viral prodrome	0 (0.00)
Cardiovascular risk factors	
Smoking (previous or current)	3 (37.50)
Drinking (5-6 drinks daily x 5-10 years)	1 (12.50)
Illicit drug use (methamphetamine, cocaine, marjuana)	0 (0.00)
Exposure to cardiac toxins (anthracyclines, trastzumab, alkylating agents)	0 (0.00)
Family history of CAD, non-ischemic HF, or SCD	0 (0.00)
Duration of corticosteroid at diagnosis	
< 1 year	5 (62.50)
> 1 year	3 (37.50)
Treatment received after diagnosis (dose, duration)	
Glucocorticoids, high-dose (≥40 mg prednisone or equivalent)	1 (12.50)
Glucocorticoids, pulse	7 (87.50)
Cyclophosphamide	0 (0.00)
Other (specify)	0 (0.00)

*SLEDAI, SLE Disease Activity Index; SD, standard deviation; CAD, coronary artery disease; HF, heart failure; SCD, sudden cardiac death. *Only 4 patients had lipid profile test results.*

Clinical features of lupus myocarditis

Orthopnea and peripheral edema were the most common symptom and the most common sign, respectively, as shown in Table II. Half of all patients had heart failure with a New York Heart Association (NYHA) classification of functional class III.

Laboratory and radiographic results

Anemia was present in all patients, and up to 50% had leukopenia. The 24-hour total urinary protein was >0.5 g/day in all patients for whom the test was done. Pleural effusion was the most common finding on chest x-ray (75%). Detailed results are summarized in Table III.

Advanced diagnostic tests

None of the patients underwent coronary angiogram, cardiac MRI, or endomyocardial biopsy.

Electrocardiographic and echocardiographic features

Details of imaging findings are shown in Tables IV and V. Sinus tachycardia was the most common ECG finding. Echocardiography showed that all patients had wall motion abnormalities, with majority having global hypokinesia. The mean LV EF was 33.6% ± 8.3%, with all patients having values of ≤44%.

Outcomes

Half of the patients required intensive care unit admission for myocarditis and ventilatory support for congestive symptoms. Complications were as follows: prerenal acute kidney injury in two patients; cardiogenic shock from acute decompensated heart failure that eventually resolved in one patient; and acute pulmonary congestion in one patient. Six out of eight patients (75%) were discharged improved. One mortality was signed out as cardiogenic shock from lupus myocarditis; this patient had concomitant septic shock from pneumonia and otitis media. She was given corticosteroids at a dose of 1 mg/kg/dose prednisone equivalent, but she expired prior to receiving MPPT. The outcome for one patient was unknown due to hospital transfer.

Discussion

Existing local literature on lupus myocarditis is limited. Studies on cardiovascular involvement in lupus used two-dimensional echocardiographic determination of cardiac abnormalities and reviews of cardiac necropsy.[3] (O. M. Samar-Sy, E. Salido, et al, unpublished data, 1993) A 2004 study showed that myocarditis is the second most common cardiac manifestation of lupus, following pericardial effusion. (M. M. Gumban and E. Salido, unpublished data, 2004) Our study looks at Filipino lupus patients who received a clinical diagnosis of myocarditis during hospital admission, prior to supportive laboratory testing and imaging.

Our patients were diagnosed with lupus myocarditis early in the course of their disease, similar to existing

Table II. Patient's presenting symptoms and clinical signs of myocarditis (n = 8)

Variable	n (%)
Symptom	
Exertional dyspnea	3 (37.50)
Dyspnea at rest	4 (50.00)
Orthopnea	6 (75.00)
Palpitations	1 (12.50)
Chest pain	4 (50.00)
Paroxysmal nocturnal dyspnea	2 (37.50)
Sign	
Jugular venous distention	2 (37.50)
Lung crackles	6 (75.00)
Tachycardia	5 (62.50)
S3 or S4	1 (12.50)
Murmurs	1 (12.50)
Peripheral edema	8 (100.00)
Blood pressure upon presentation	
BP ≥ 140 mmHg systolic	2 (37.50)
BP > 90 and <140 mmHg systolic	4 (50.00)
BP < 90 mmHg systolic and/or cardiogenic shock	2 (37.50)
NYHA classification	
FC I	0 (0.00)
FC II	2 (37.50)
FC III	4 (50.00)
FC IV	2 (37.50)
Acute heart failure (<2 weeks duration)	
Yes	2 (25.00)
No	6 (75.00)

NYHA, New York Heart Association; FC, functional class.

Table III. Laboratory and radiographic results at the time of diagnosis of myocarditis

Variable	n/total done	% positive
Complete blood count		
Anemia (Hemoglobin <120 g/L)	8/8	100
Leukopenia (WBC <4000/mm^3)	4/8	50
Neutropenia (Absolute neutrophil count <1000/mm^3)	0/8	0
Lymphopenia (Absolute lymphocyte count <1000/mm^3)	2/8	25
Thrombocytopenia (platelet <100,000/mm^3)	2/8	25
Blood chemistry		
Creatinine >92 umol/L	4/8	50
Albumin <30 g/L	8/8	100
Total cholesterol ≥200 mg/dL	1/4	25
Triglycerides ≥150 mg/dL	3/4	75
HDL <50 mg/dL	3/4	75
LDL ≥100 mg/dL	1/4	25
Troponin I ≥15.6 ng/L	3/4	75
Urine studies		
24-hour total protein >0.5 g/24 h	5/5	100
Immunology		
Anti-dsDNA >15 IU/mL	4/5	80
Serum C3 <0.89 g/L	2/4	50
Chest x-ray		
Cardiomegaly	5/8	62.5
Pulmonary vascular congestion	3/8	37.5
Pleural effusion	6/8	75

WBC, white blood cell; eGFR, estimated glomerular filtration rate; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; HDL, high-density lipoprotein; LDL, low density lipoprotein; ANA, antinuclear antibody; anti-dsDNA, anti-double stranded deoxyribonucleic acid; C3, complement component C3.

Table IV. Patients' electrocardiogram findings on presentation (n = 8)

Variable	n (%)
Heart Rate	
None	2 (25)
Sinus tachycardia	6 (75)
Sinus bradycardia	0 (0)
PR abnormalities	
PR shortening	0 (0)
PR prolongation	0 (0)
QRS width	
<120 msec	8 (100)
120-150 msec	0 (0)
>150 msec	0 (0)
QT prolongation	0 (25)
ST changes	
None	1 (12.5)
Nonspecific ST depression	5 (62.5)
Nonspecific early repolarization	0 (0)
Significant ST depression	1 (12.5)
Significant ST Elevation	1 (12.5)
T-wave changes	5 (62.5)
Ventricular arrhythmias	0 (0)
Low-grade ectopies	0 (0)
VT	0 (0)
Supraventricular arrhythmias	0 (0)
Low grade ectopies	0 (0)
AF	0 (0)
Other SVT	0 (0)
Bundle branch blocks	0 (0)
AV blocks	0 (0)
Other heart blocks	0 (0)

VT, ventricular tachycardia; AF, atrial fibrillation; SVT supraventricular tachycardia

literature showing a disease duration ranging from three to 20 months at the time of myocarditis.[7,9,12] Consistent also with case-control studies are the higher prevalence of hematologic and renal involvement, as well as higher disease activity measured with SLEDAI among myocarditis patients.[7,9,12] (O. M. Samar-Sy, E. Salido, et al, unpublished data, 1993) The high mean corticosteroid dose of 116.88 mg/day prednisone equivalent in our study is consistent with the presence of high lupus disease activity at the time myocarditis was diagnosed. As for anti-dsDNA, its prevalence in lupus myocarditis did not appear to differ from that in the general lupus population.[8,13,14]

Consistent with previous reports, orthopnea was the most common presenting symptom of myocarditis, with peripheral edema and lung crackles as the most common signs.[7,8] However, as six out of the eight patients with peripheral edema had concomitant nephritis, it was difficult to attribute the edema to myocarditis alone.

Half of our patients had heart failure with NYHA functional class III, almost similar to a study showing functional class III or IV in 80%.[10] Only two patients presented with acute heart failure, and both were eventually discharged in a stable condition.

Table V. Patients' echocardiogram findings on presentation (n = 8)

Variable	n (%)
Extent of LV wall motion abnormalities	
Regional	3 (37.5)
Global	5 (62.5)
Severity of LV wall motion abnormalities	
Mild hypokinesia	2 (25)
Moderate hypokinesia	3 (37.5)
Severe hypokinesia	3 (37.5)
Global LV systolic function (LV ejection fraction)	
<30%	3 (37.5)
30-34%	1 (12.5)
35-39%	2 (25)
40-44%	2 (25)
45-49%	0 (0)
50-54%	0 (0)
>54%	0 (0)
Tissue Doppler findings (n = 6)	
Normal mitral annular velocities	1 (16.7)
Reduced and/or reversed velocities	0 (0)
Increased E/e' ratio (>8)	5 (83.3)
RV involvement	0 (0)
Diastolic function	
Normal diastolic function	1 (12.5)
Grade I diastolic dysfunction	2 (25)
Grade II diastolic dysfunction	1 (12.5)
Grade III/IV diastolic dysfunction	4 (50)
Pericardial effusion	
None	3 (37.5)
Minimal/mild	3 (37.5)
Moderate	1 (12.5)
Large	1 (12.5)

LV, left ventricular; RV, right ventricular; E/e' ratio, mitral peak velocity of early filling (E) to early diastolic mitral annular velocity (e') as a measure of left ventricular diastolic dysfunction (in normal individuals, the ratio is <8).

As in the literature, sinus tachycardia, nonspecific ST segment depression, and T-wave abnormalities (specifically inversion) were the most common ECG findings.[9] It should be noted, however, that ECG changes in myocarditis are nonspecific and insensitive.[15] None of our patients were documented to have arrhythmias or bundle branch blocks, which were found in other studies as a rare complication of myocarditis.[10] Chest x-ray showed pleural effusion and cardiomegaly in most patients, similar to other studies.[8] The utility of the chest x-ray in diagnosing myocarditis is mostly for exclusion of other possible explanations for the presenting symptoms.

It has been shown that abnormal echocardiogram findings are seen as early as five months into lupus among newly diagnosed patients.[4] At this stage, myocardial involvement is seen only in 20%. Later in the course of the disease, its prevalence may increase to 74%, especially with higher doses of and longer exposure to corticosteroid therapy. (O. M. Samar-Sy, E. Salido, et al, unpublished data, 1993) Most of our patients were found to have global and moderate to severe hypokinesia of the LV wall, and were on high to very high doses of corticosteroids[11] at the time of

diagnosis of myocarditis. The local study cited above also found that prolonged exposure to high-dose steroids resulted in LV systolic dysfunction and LV dilatation. Cardiovascular effects of steroid therapy were shown to manifest after six months to one year of treatment.[2] As three of our patients were on steroid therapy for more than one year, the effect of steroids on the myocardial function of these patients could not be excluded.

Left ventricular wall hypokinesis, especially if global, is strongly suggestive of myocarditis among lupus patients in the absence of other known causes.[7] Global hypokinesia pointing to diffuse involvement of the myocardium was seen in five out of eight patients in our study. As observed in other studies,[16] acute myocarditis may also present with regional hypokinesia from impairment of right ventricular relaxation by moderate to large pleural effusions. However, coronary artery disease cannot be totally ruled out in such cases without coronary angiography or myocardial perfusion imaging.[17]

In our study, MPPT was the treatment of choice for myocarditis, as was previously shown in a local study.[18] High dose corticosteroids in the form of either one mg/kg/day prednisone equivalent or MPPT have been used as first-line treatment.[7] Other agents like cyclophosphamide, mycophenolate mofetil, azathioprine, intravenous immunoglobulin, and rituximab have also been shown to benefit patients with this condition along with high-dose steroids, but these have not been used for lupus myocarditis in our institution to date.[19-23]

Consistent with the literature, outcomes of lupus myocarditis were favorable after early immunosuppressive therapy, with most patients achieving clinical improvement within one to four weeks of treatment.[7,12,24] The sole mortality in our study had concomitant septic shock from pneumonia and otitis media. Findings from the multiethnic United States cohort LUMINA (LUpus in Minorities: NAture vs nurture) show that lupus patients with myocarditis have the same prognosis as those without it for the first five years of disease, but survival rates drastically decrease in the myocarditis cohort. It is postulated that myocarditis in these patients influence mortality indirectly through higher damage accrual, as measured in this population using the SLICC damage index.[12] It has been shown that longer SLE duration (eight to 21 years), a lower absolute lymphocyte count, use of prednisone at doses of at least 0.5 mg/kg/day, and presentation with a low LV ejection fraction without improvement after therapy may all contribute to a much higher mortality rate.[8,9]

Limitations of this study include its retrospective design and the lack of confirmation of lupus myocarditis with endomyocardial biopsy. In addition, the disease burden may be higher in a study of hospitalized patients.

Two patients did not have data on TDI due to the lack of this feature in one of two echocardiography machines used (General Electric Vivid E9 with TDI and General Electric Vivid 7 without TDI). In addition, because echocardiography was performed by different operators, standardization of echocardiographic readings could not be assured. Diagnostic certainty is similarly hampered by the lack of data on coronary angiogram, cardiac MRI, and endomyocardial biopsy findings. These modalities may help confirm or rule out coexisting coronary artery disease, vasculitis, and/or thromboembolism.

A study with a larger sample size and prospective design is needed to more reliably determine disease outcomes and establish associations between these and identified risk factors. Inclusion of post-treatment echocardiography in future studies will serve as an objective measure of the clinical improvement observed with therapy. Long-term follow up of lupus patients with subclinical myocarditis is also recommended to determine whether or not this is predictive of clinically significant myocarditis, and if early treatment will alter outcomes.

Conclusion

The clinical profile and outcomes of Filipino lupus patients diagnosed with myocarditis are comparable to that of international literature. Patients presented with clinical myocarditis early in the course of lupus. They had high lupus disease activity, mostly in the form of hematologic activity and nephritis with requirement for high-dose corticosteroids. Majority of patients had moderate to severe and global hypokinesia of the LV wall. Outcomes are generally favorable with early immunosuppressive therapy, with MPPT as the most common treatment.

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I. Appendix

A. 1997 Update of the 1982 American College of Rheumatology (ACR) revised criteria for classification of systemic lupus erythematosus
Classify the patient as having SLE if any 4 or more of the following 11 criteria are present, serially or simultaneously, during any interval of observation.

Descriptor	Definition
Malar rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
Discoid rash	Erythematous, raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by physician
Nonerosive arthritis	Involving two or more peripheral joints, characterized by tenderness, swelling, or effusion
Serositis	Pleuritis: convincing history of pleuritic pain or rubbing heard by a physician or evidence of pleural effusion or Pericarditis: documentation on electrocardiography, rubbing, or evidence of pericardial effusion
Renal disorder	Persistent proteinuria: greater than 0.5 g per day or greater than 3+ if quantitation not performed or Cellular casts: may be red blood cell, hemoglobin, granular, tubular, or mixed
Neurologic disorder	Seizures: in the absence of offending drugs or known metabolic derangements (e.g., uremia, ketoacidosis, electrolyte imbalance) or Psychosis: in the absence of offending drugs or known metabolic derangements (e.g., uremia, ketoacidosis, electrolyte imbalance)
Hematologic disorder	Hemolytic anemia: with reticulocytosis or Leukopenia: lymphocyte count less than 4,000 per µL (4×10^9 per L) on two or more occasions or Lymphopenia: lymphocyte count less than 1,500 per µL (1.5×10^9 per L) on two or more occasions or Thrombocytopenia: platelet count less than 100×10^3 per µL (100×10^9 per L) in the absence of offending drugs
Immunologic disorder	Anti-DNA: antibody to native DNA in abnormal titer or Anti-Sm: presence of antibody to Sm nuclear antigen or Positive finding of antiphospholipid antibodies based on one of the following: • An abnormal serum level of immunoglobulin G or immunoglobulin M anticardiolipin antibodies • A positive test result for lupus anticoagulant using a standard method • A false-positive serologic test result for syphilis known to be positive for at least six months and confirmed by Treponema pallidum immobilization or fluorescent treponemal antibody absorption test
ANA	An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs known to be associated with drug-induced lupus

From Hochberg MC. 1997 Update of the 1982 American College of Rheumatology revused criteria for classification of systemic lupus erythematosus [letter]. Arthritis Rheum 1997;40:1725.

B. 2012 Systemic Lupus International Collaborating Clinics (SLICC) classification criteria
Classify the patient as having SLE if he or she meets the following:
a) ≥4 criteria or biopsy-proven lupus nephritis with positive ANA or anti-dsDNA
b) ≥1 clinical and 1 immunologic criteria is required for classification as SLE

Descriptor	Definition
Clinical Criteria	
Acute cutaneous lupus	Lupus malar rash (do not count if malar discoid), Bullous lupus, Toxic epidermal necrolysis variant of SLE, Maculopapular lupus rash. Photosensitive lupus rash (in the absence of dermatomyositis). Subacute cutaneous lupus (nonindurated psoriaform and/or annular polycyclic lesions that resolve without scarring, occasionally with post- inflammatory dyspigmentation or telangiectasias)
Chronic Cutaneous Lupus	Classical discoid rash-localised (above the neck) or generalised (above and below the neck).Hypertrophic (verrucous)lupus. Lupus panniculitis (profundus). Mucosal lupus. Lupus erythematosus tumidus, Chillblains lupus, Discoid Lupus-lichen planus overlap.
Oral ulcers	Palate, Buccal, Tongue or Nasal ulcers (in the absence of other causes, such as vasculitis, Behcets, infection (herpes), IBD, reactive arthritis, and acidic foods)
Non-scarring alopecia	Diffuse thinning or hair fragility with visible broken hairs (in the absence of other causes such as alopecia areata, drugs, iron deficiency and androgenic alopecia)
Synovitis involving ≥2 joints	Characterized by swelling or effusion or tenderness in 2 or more joints and thirty minutes or more of morning stiffness
Serositis	Typical pleurisy for more than 1 day or pleural effusions or pleural rub Typical pericardial pain (pain with recumbency improved by sitting forward) for more than 1 day or pericardial effusion or Pericardial rub or pericarditis by ECG (in the absence of other causes, such as infection, uremia, and Dressier's pericarditis)
Renal manifestations	Urine protein/creatinine (or 24 hr urine protein) representing 500 mg of protein in 24 hr or red blood cell casts
Neurological manifestations	Seizures, psychosis, Mononeuritis multiplex (in the absence of other known causes such as primary vasculitis), myelitis, peripheral or cranial neuropathy (in the absence of other known causes such as primary vasculitis, infection and diabetes mellitus), acute confusional state (in the absence of other causes, including toxic-metabolic, uremia, drug)
Hemolytic anemia	
Leucopenia/lymphopenia	Leucopenia <4000mm3 at least once (in the absence of other known causes such as Felty's, drugs, and portal hypertension) Lymphopenia <1000mm3 at least once (in the absence of other known causes such as corticosteroids, drugs and infection)
Thrombocytopenia	<100,000mm3 at least once (in the absence of other known causes such as drugs, portal hypertension, and TTP)
Immunologic Criteria	
ANA	Above the reference range of the laboratory
Anti-dsDNA	Above laboratory reference range, except ELISA: twice above laboratory reference range
Anti-Sm	
Antiphospholipid antibody	Lupus anticoagulant, False positive RPR, Medium or high titer anticardiolipin (IgA, IgG or IgM) and beta 2-glycoprotein I (IgA, IgG or IgM)
Low complement	Low C3, C4 or CH50
Direct Coombs Test	In the absence of hemolytic anemia

From Petri M, Orbai AM, Alarcón GS, Gordon C, et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum 2012;64:2677-2686.

c. The Safety of Estrogens in Lupus National Assessment - Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI)
Formulas are as follows:
≤3: No flare present
>3-12: Mild or moderate flare
>12: Severe flare

Weighted score	Descriptor	Definition
8	Seizure	Recent onset. Exclude metabolic, infectious, or drug-related causes.
8	Psychosis	Altered ability to function in normal activity due to severe disturbance in the perception of reality. Includes halluci- nations; incoherence; marked loose associations; impoverished thought content; marked illogical thinking; bizarre, disorganized or catatonic behavior. Exclude the presence of uremia and offending drugs.
8	Organic brain syndrome	Altered mental function with impaired orientation or impaired memory or syndrome other intellectual function, with rapid onset and fluctuating clinical features. Includes a clouding of consciousness with a reduced capacity to focus and an inability to sustain attention on environment, and at least two of the following: perceptual disturbance, incoherent speech, insomnia or daytime drowsiness, increased or decreased psychomotor activity. Exclude metabolic, infectious, and drug-related causes.
8	Visual	Retinal changes from systemic lupus erythematosus: cytoid bodies, retinal hemorrhages, serous exudates or hemor- rhages in the choroid, optic neuritis (not due to hypertension, drugs, or infection).
8	Cranial nerve	New onset of a sensory or motor neuropathy involving a cranial nerve.
8	Lupus headache	Severe, persistent headache; may be migranous; unresponsive to narcotics.
8	Cerebrovascular accident	New syndrome. Exclude arteriosclerosis.
8	Vasculitis	Ulceration, gangrene, tender finger nodules, periungual infarction, splinter hemorrhages. Vasculitis confirmed by biopsy or angiogram.
4	Arthritis	More than 2 joints with pain and signs of inflammation .
4	Myositis	Proximal muscle aching or weakness associated with elevated creatine phosphokinase/aldolase levels, electromyo- graphic changes, or a biopsy showing myositis.
4	Casts	Heme, granular, or erythrocyte.
4	Hematuria	More than 5 erythrocytes per high-power field. Exclude other causes (stone, infection).
4	Proteinuria	More than 0.5 grams of urinary protein excreted per 24h. New onset or recent increase of > 0.5 g/24h.
4	Pyuria	More than 5 leukocytes per high-power field. Exclude infection.
2	New malar rash	New onset or recurrence of an inflammatory type of rash.
2	Alopecia	New or recurrent. Apatch of abnormal, diffuse hair loss.
2	Mucous membranes	New onset or recurrence of oral or nasal ulcerations.
2	Pleurisy	Pleuritic chest pain with pleural rub or effusion, or pleural thickening.
2	Pericarditis	Pericardial pain with at least one of rub or effusion. Confirmation by electro- or echocardiography.
2	Low complement	A decrease in CH50, C3, or C4 level (to less than the lower limit of the laboratory-determined normal range).
2	Increased DNA binding	More than 25% binding by Farr assay (to >the upper limit of the laboratory-determined normal range, e.g. 25%).
2	Fever	More than 38 oC after the exclusion of infection.
2	Thrombocytopenia	Fewer than 100,000 platelets
2	Leukopenia	Leukocyte count of <3000/mm3 (not due to drugs)

From Petri M, Kim MY, Kalunian KC, et al. Combined oral contraceptives in women with systemic lupus erythematosus. N Engl J Med 2005;353:2550-8.