Chapter 99

Redefining Lupus in 2012

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INTRODUCTION: THE CIRCULAR ARGUMENT

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease affecting multiple organ systems with protean manifestations. A gold standard does not exist for the diagnosis of SLE. Clinical presentations and organ involvement vary widely and SLE is diagnosed by recognizing a typical pattern. The disease varies among patients and within patients, and patterns change over time.[1] There is often a significant delay in diagnosis due to this range of presentation.[2] Because of the lack of a gold standard and difficulty of defining SLE, diagnostic criteria must be constructed in a circular manner by testing variables against a diagnosis established by intuition. The "best" criteria therefore only describe the current conventional wisdom in an efficient manner.[3] Lets take a look at the case scenarios in **Table 1**. Do these patients have lupus?

As clinicians are familiar with the classification criteria of lupus where 4 of the 11 criteria should be positive, none of these patients fulfill the criteria.[4] However, we do know intuitively that there is a high chance that these patients may have SLE. Actually all of them did have lupus but would not have been diagnosed with the current criteria.

Scenarios like the ones above have concerned rheumatologists ever since the first classification criteria for SLE were published in 1971 by Cohen et al.[5] They required the presence of 4 of 14 criteria for the classification of SLE. In 1982, Tan et al. revised the criteria to reflect changes since 1960s, especially serologic tests, including antinuclear antibody (ANA) and anti-dsDNA, and to employ computer-based techniques for criteria development.[6] These were revised again in 1997, but never validated. This article attempts to highlight the pitfalls in the existing criteria and highlights the new criteria for SLE proposed in 2012.

TABLE 1 | Do these patients have SLE?

Clinical scenarios
1. A 26-year-old woman was diagnosed as having possible multiple sclerosis. She suffered visual symptoms and speech disturbance. However, she also complained of arthralgia and fatigue. She tested positive for ANA. Does she have lupus?
2. A 24-year-old lady presented with acute onset of facial puffiness, edema, microscopic hematuria and proteinuria. Renal biopsy showed endocapillary lesions with mesangial deposits with IIF staining for IgG, IgA and IgM. She was positive for ANA. Does she have lupus?
3. An 18-year-old patient presented with hemolytic anemia and was positive for ANA, anti-dsDNA and anti-Sm. Does she have lupus?
4. A 34-year-old lady presented with synovitis of 6 weeks duration affecting PIPJ and MCPJ, had a platelet count of 95,000. She was ANA and APLA positive. Does she have lupus?

Abbreviations: SLE, Systemic lupus erythematosus; ANA, Antinuclear antibody; IIF, Indirect immunofluorescence; PIPJ, Proximal interphalangeal joint; MCPJ, Metacarpophalangeal joint; APLA, Antiphospholipid antibody; anti-Sm, Anti-Smith

CLASSIFICATION VERSUS DIAGNOSTIC CRITERIA

The American Rheumatism Association (ARA) criteria were called "criteria for classification" as they were not meant to be exclusive or restrictive.[7] However, these criteria have virtually replaced all other definitions of SLE and have been extensively used by authors for diagnosis and inclusion in their studies, thereby effectively restricting the diagnosis of SLE. Canoso in 1979 reviewed the literature citing the 1971 classification criteria and pointed out that a large number of studies had used the criteria diagnostically rather than as a method of classification.[8] By the time four criteria have been identified, a patient is likely to have had the disease longer, be older and perhaps have more end-organ damage as a consequence of disease activity than a patient who has only recently been diagnosed.[9]

Tan et al. in their original description, caution that the criteria cannot be used as truly diagnostic until more extensive tests against a wider variety of diseases have been conducted. However, they did not specify the kind of evidence that may support or prevent diagnostic application of the criteria or necessitate review. They stress that the criteria have been deliberately kept simple in order to facilitate teaching and practical application. Currently, the American College of Rheumatology (ACR) criteria are only meant to be used for clinical trials.

However, this distinction between clinical trials and therapeutic reality is misleading. Inference from clinical trials is only possible to the population that has participated in these trials. The same is true for epidemiologic studies. Therefore, the consistent use of the criteria in clinical trials essentially defines diseases. This is exactly what happened, as the literature using the criteria shows.

PITFALLS/UNMET NEEDS

What are the unmet needs that justify new classification criteria for SLE, antiphospholipid syndrome (APS) and chronic cutaneous lupus?[10]

- The 1982 criteria are overly biased and weighted toward cutaneous lupus, with four cutaneous criteria (all other organ systems have one each). However, the new treatments under development for SLE are largely directed against major (i.e. renal) organ involvement. Thus, separate criteria and validation are required for chronic cutaneous lupus and APS.
- Hypocomplementemia (omitted in the 1982 criteria) has been shown to be one of the single most powerful criteria for SLE.[11] Exclusion of hypocomplementemia may prevent "classification" of patients who truly have SLE, thus limiting the potential number

of patients available for clinical trials. This is especially important for studies recruiting renal lupus patients who frequently have hypocomplementemia.

- Advances have been made in autoantibody assays, such as the antiphospholipid, anti-dsDNA and anti-Sm antibodies. The criterion for antiphospholipid antibodies has not been subjected to validation, and its inclusion may lead to confusion between SLE and primary APS. The appropriateness of new commercial enzyme-linked immunosorbent assay (ELISA) for anti-DNA has not been evaluated.
- Many of the existing criteria require redefinition and refinement based on current practice. This is especially relevant for the renal and neurologic criteria (only psychosis and seizure are included), not beginning to reflect the breadth of neurologic lupus, as noted by the ACR neurologic classification criteria.[12]
- Future criteria must be generalizable to multiple ethnic groups and be internationally valid. Different frequencies of individual criteria for different ethnicities have already been shown for African-Americans and for Japanese.
- Future criteria need to include input from nonrheumatology specialists who frequently care for and diagnose lupus, including dermatologists, neurologists and nephrologists.
- Systemic lupus erythematosus is likely a disease with multiple subsets. Accurate classification criteria would allow future clinical trials to look at treatment variability by subset, including chronic cutaneous lupus and APS.

REDEFINING LUPUS IN 2012

The Systemic Lupus International Collaborating Clinics (SLICC) Classification 2012 criteria were derived using the technique of "recursive partitioning" to derive a relatively simple classification rule.[13] The diagnosis of SLE is as per **Tables 2** and **3**.

TABLE 2 | Classifying SLE as per SLICC criteria 2012

Classify a patient as having SLE if
• The patient satisfies four of the criteria listed in Table 3 including at least one clinical criterion and one immunologic criterion; or
• The patient has biopsy-proven nephritis compatible with SLE and with ANA or anti-dsDNA antibodies.

Abbreviations: SLE, Systemic lupus erythematosus; SLICC, Systemic Lupus International Collaborating Clinics Classification; ANA, Antinuclear antibody

TABLE 3 | Clinical and immunologic criteria used in the SLICC classification criteria

Clinical criteria	
Acute cutaneous lupus	Including 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; or subacute cutaneous lupus (nonindurated psoriaform and/or annular polycyclic lesions that resolve without scarring, although occasionally with postinflammatory depigmentation or telangiectasia)
Chronic cutaneous lupus	Including classical discoid rash; localized (above the neck); generalized (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, Behçet's, infection (herpes), inflammatory bowel disease, reactive arthritis and acidic foods
Nonscarring 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 two or more joints, characterized by swelling, effusion or tenderness in two or more joints, and 30 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 electrocardiography in the absence of other causes, such as infection, uremia and Dressler's pericarditis
Renal	Urine protein/creatinine (or 24-hour urine protein) representing 500 mg of protein/24 hour or red blood cell casts
Neurologic	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, drugs
Hemolytic anemia	
Leukopenia	< 4,000/mm^3 at least once (in the absence of other known causes such as Felty's, drugs and portal hypertension); or Lymphopenia (< 1,000/mm^3 at least once) in the absence of other known causes such as corticosteroids, drugs and infection
Thrombocytopenia	(< 100,000/mm^3) at least once (in the absence of other known causes such as drugs, portal hypertension, and TTP)
Immunologic criteria	
ANA	Above laboratory reference range
Anti-dsDNA	Above laboratory reference range, except ELISA: twice above laboratory reference range
Anti-Sm	
Antiphospholipid antibody	Any of the following lupus anticoagulant false-positive RPR medium or high titer anticardiolipin (IgA, IgG or IgM) anti-β2 glycoprotein I (IgA, IgG or IgM)
Low complement	Low C3, low C4, low CH50
Direct Coombs test	In the absence of hemolytic anemia

Criteria are cumulative and need not be present concurrently.

Abbreviations: SLE, Systemic lupus erythematosus; SLICC, Systemic Lupus International Collaborating Clinics Classification; ANA, Antinuclear antibody; ELISA, Enzyme linked immunosorbent assay; RPR, Rapid plasma reagin

TABLE 4 | Performance of the proposed classification as compared to the current ACR criteria on the derivation sample based on 702 cases

Rule	"Sensitivity"*	"Specificity"**	Misclassified cases (number)
1997 ACR criteria***	267/310 (86%)	365/392 (93%)	70
SLICC criteria	292/310 (94%)	361/392 (92%)	49

*"Sensitivity": Of those that were 80% consensus SLE, proportion (%) correctly classified by the criteria as SLE.
**"Specificity": Of those that were 80% consensus not SLE, proportion (%) correctly classified by the criteria as not SLE.
*** ACR criteria are based on satisfying 4 of 11 criteria.

Abbreviations: ACR, American College of Rheumatology; SLICC, Systemic Lupus International Collaborating Clinics Classification

The new criteria effectively address the pitfalls mentioned above. Lupus nephritis alone with ANA positivity can be classified as SLE. Hypocomplementemia becomes an important component while multiple neurological syndromes like myelitis and mononeuritis multiplex have been included.

How does the new criteria perform vis a vis the older 1997 modification of 1982 criteria. As **Table 4** shows, the sensitivity is significantly improved with no loss of specificity.

CONCLUSION

Since the original criteria for lupus, first proposed in 1971, three significant revisions have taken place. The 1982 criteria (revised in 1997) continue to be the most widely used. Although developed as "classification criteria", they have been extensively used as diagnostic criteria. Over a period of time, many pitfalls became evident and the current revision in 2012 by SLICC using the methodology of recursive partitioning has attempted to overcome the same. The new criteria retain the specificity while being more sensitive. As with original ACR criteria they have not been tested for purposes of diagnosis. SLICC concludes that the new criteria retain the goal of simplicity of use, yet reflect current knowledge of SLE obtained in 29 years since the initial ACR criteria.

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