Validation of the Systemic Lupus International Collaborating Clinics classification criteria in a cohort of patients with full house glomerular deposits

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In 2012, the Systemic Lupus International Collaborating Clinics (SLICC) presented a new classification for systemic lupus erythematosus (SLE). In this classification, biopsy-confirmed lupus nephritis with positive antinuclear or anti-double-stranded DNA antibodies became a stand-alone criterion. Because of the unknown diagnostic performance among patients from nephrology clinics, we aimed to test the validity of the SLICC classification, compared with the American College of Rheumatology classification, in a cohort of patients whose renal biopsies would raise the clinicopathologic suspicion of lupus nephritis. All patients with a renal biopsy showing full house glomerular deposits and clinical follow-up in our center were included and reevaluated, after which clinicians and a pathologist reached a consensus on the reference-standard clinical diagnosis of SLE. The diagnostic performance and net reclassification improvement were assessed in 149 patients, 117 of whom had clinical SLE. Compared with the American College of Rheumatology classification, the SLICC classification had better sensitivity (100 *vs*. 94%); although, this was at the expense of specificity (91 *vs*. 100%; net reclassification improvement −0.03). Excluding the stand-alone renal criterion, the specificity of the SLICC classification reached 100%, with a significant net reclassification improvement of 0.06 compared with the American College of Rheumatology classification. The SLICC classification performed well in terms of diagnostic sensitivity among patients with full house glomerular deposits; whereas, the stand-alone renal criterion had no additional value and compromised the specificity. Thus, presumed patients with lupus nephritis in nephrology clinics reflect a distinct SLE disease spectrum warranting caution when applying SLE classification criteria.

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Systemic lupus erythematosus (SLE) is a complex autoimmune disease with diverse clinical manifestations and presenting symptoms that have considerable overlap with other diseases.[1] SLE classification criteria have been designed to create homogeneous groups of SLE patients to conduct collaborative and reproducible research. Although SLE classification criteria have been designed for research purposes, they are often used for the purpose of diagnosis in clinical practice. The focus of SLE classification criteria has traditionally been on patients encountered in rheumatology clinics, although a need for input from nonrheumatology specialists who frequently see lupus patients was recognized.[2] This may be particularly relevant to nephrologists, because patients with renal biopsy findings reminiscent of lupus nephritis (LN) would readily be evaluated in light of these criteria to confirm the diagnosis. The recent descriptions of entities including "renal-limited lupus-like nephritis,"[3] and idiopathic[4,5] and secondary "nonlupus full house nephropathy"[4–10] stress the importance of valid SLE classification criteria in the nephrology clinic: to help distinguish LN patients based on clinical and laboratory findings.

The importance of valid SLE classification criteria in the nephrology clinic recently gained attention by the increased weight that was attributed to renal lupus in the Systemic Lupus International Collaborating Clinics (SLICC) 2012 classification.[11] In the SLICC classification,[11] biopsy-confirmed LN in the presence of antinuclear antibodies (ANA) or anti-double-stranded DNA (anti-dsDNA) antibodies was introduced as an exception to the conventional requirement of ≥4 criteria employed in the original[12] and updated[13] American College of Rheumatology (ACR) classifications. Remarkably, the definition of biopsy-confirmed LN was unspecified in both the ACR and the SLICC classifications, and firm criteria for biopsy-confirmed LN in the histopathological classification referred to are missing.[14]

In light of the increased weight of renal lupus in the SLICC classification and the unknown diagnostic performance of the classification in patients from nephrology clinics, we aimed to test the validity of the SLICC classification in a cohort of patients whose renal biopsies would raise the clinicopathologic suspicion of LN. Because the definition of "biopsy-confirmed" LN is left open to interpretation, we selected our cohort based on a biopsy feature characteristic of LN—so as to raise the clinicopathologic suspicion—but concise enough to identify a consistent cohort. From a nephropathologic perspective, the finding of a "full house" pattern of immunofluorescence, with concurrent positive glomerular staining for IgA, IgG, IgM, C3, and C1q, would certainly raise the possibility of SLE as a differential diagnostic consideration warranting the evaluation of clinical criteria. Here, we tested the validity of the SLICC compared with the ACR classification criteria to distinguish SLE patients with full house glomerular deposits. Moreover, we studied additional biopsy findings that may distinguish SLE patients in this setting. This is the first validation study of the SLICC classification in a cohort selected on the basis of renal biopsy findings raising the clinicopathologic suspicion LN, reflecting a diagnostic problem area encountered in the nephrology clinic.

RESULTS

A total of 149 patients with renal biopsies fulfilling our inclusion criteria were identified from the pathology archives between 13 August 1968 and 9 July 2014. Fourteen patients were biopsied before 1980, 32 from 1980 to 1989, 47 from 1990 to 1999, 42 from 2000 to 2009, and 14 from 2010 to 2014.

Reference standard clinical diagnosis of SLE

According to clinicians' and a pathologist's expert opinions, 117 of 149 patients fulfilled the diagnosis SLE at the time of biopsy. These diagnoses composed the reference standard; these patients will be referred to hereafter as patients with "clinical SLE." Of the patients with clinical SLE, renal involvement first appearing at the time of renal biopsy was the decisive factor establishing the clinical diagnosis in 40 patients. In addition, 75 patients had a clinical diagnosis of SLE prior to renal biopsy. For 2 patients, the time since onset of SLE could not be retrieved from the records. The median time between SLE diagnosis and renal biopsy was 1.4 years (interquartile range [IQR]: 0–5.3). For all patients with clinical SLE at the time of renal biopsy, the diagnosis was confirmed by the clinical course during follow-up (median: 10.6 years [IQR: 4.9–18.4]). None of the 32 of 149 patients without clinical SLE at the time of renal biopsy were clinically diagnosed with SLE during median follow-up of 20.0 years (IQR: 8.3–33.8). The consensus clinicopathologic diagnoses of these 32 patients were membranous nephropathy (anti-phospholipase A2 receptor–positive, $n = 1$; cancer-associated, $n = 3$), IgA nephropathy ($n = 4$), infection-related glomerulonephritis ($n = 2$), antineutrophil cytoplasmic antibody–associated glomerulonephritis ($n = 2$), and idiopathic non–lupus full house nephropathy ($n = 20$).[5] Details on the clinical presentation, biopsy findings, and clinical follow-up of these patients are provided elsewhere.[5]

General characteristics of patients with and without clinical SLE

General characteristics of patients in our cohort and the prevalence of individual ACR and SLICC classification criteria are shown in Table 1. Patients with clinical SLE were significantly younger and more often female than were patients without clinical SLE. For some patients, the absence or presence of cutaneous or immunologic criteria or both was unconvincing; in these cases, these criteria were excluded from the comparisons. The 32 patients without clinical SLE less frequently fulfilled individual ACR and SLICC classification criteria than did the 117 patients with clinical SLE,

Table 1 | General characteristics and prevalence of individual 1997 ACR[a] and 2012 SLICC[b] criteria in patients with and without clinical SLE in the full house cohort

Characteristics	Clinical SLE ($n = 117$)	No clinical SLE ($n = 32$)	*P* value
Age (yr), mean ± SD	32.6 ± 14.6	38.7 ± 16.2	0.041
Sex, male:female	30:87	21:11	<0.001
ACR criteria, median (IQR)	5 (3, 9)	1 (1, 3)	<0.001
SLICC criteria, median (IQR)	7 (4, 14)	1 (1, 3)	<0.001
	***n*/total (%)**	***n*/total (%)**	
Clinical criteria			
Acute/subacute cutaneous lupus[b]	66/117 (56.4)	0/32 (0)	<0.001
Malar rash[a]	48/112 (42.9)	0/32 (0)	<0.001
Photosensitivity[a]	25/112 (22.3)	0/32 (0)	0.001
Chronic cutaneous lupus[b]	14/117 (12.0)	0/32 (0)	0.041
Discoid rash[a]	11/106 (9.4)	0/32 (0)	0.122
Nonscarring alopecia[b]	21/117 (17.9)	0/32 (0)	0.008
Oral/nasal ulcers[a,b]	25/117 (21.4)	3/32 (9.4)	0.200
Arthritis[a,b]	86/117 (73.5)	1/32 (3.1)	<0.001
Serositis[a,b]	44/117 (37.6)	1/32 (3.1)	<0.001
Neurological disorder[a,b]	18/117 (15.4)	0/32 (0)	0.013
Hemolytic anemia[a,b]	20/117 (17.1)	0/32 (0)	0.008
Lymphopenia/ leukopenia[a,b]	36/117 (30.8)	0/32 (0)	<0.001
Thrombocytopenia[a,b]	28/117 (23.9)	0/32 (0)	0.001
Immunologic criteria			
Antinuclear antibody[a,b]	116/117 (99.1)	3/26 (11.5)	<0.001
Anti-dsDNA[a,b]	80/109 (73.4)	0/28 (0)	<0.001
Anti-Sm[a,b]	18/56 (32.1)	0/8 (0)	0.093
Antiphospholipid antibody[a,b]	41/81 (50.6)	0/5 (0)	0.057
Hypocomplementemia[b]	94/109 (86.2)	2/23 (8.7)	<0.001
Direct Coombs test[b]	25/75 (33.3)	0/13 (0)	0.016

ACR, American College of Rheumatology; Anti-dsDNA, anti-double-stranded DNA antibody; anti-Sm, anti-Smith antibody; IQR, interquartile range; SLE, systemic lupus erythematosus; SLICC, Systemic Lupus International Collaborating Clinics.
Classification criteria were registered up to and including the time of renal biopsy. Fractions indicate the number of patients with a particular criterion divided by the total number of patients for whom the presence or absence of a criterion could be retrieved. The total number of SLE classification criteria was compared using Mann-Whitney *U* test. The prevalences of individual SLE criteria were compared using Fisher exact tests.
[a]ACR criteria.
[b]SLICC criteria.