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## Development of SLE among “Potential SLE” Patients Seen in Consultation: Long-Term Follow-Up

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### Abstract

**Objective**—To identify factors associated with development of systemic lupus erythematosus (SLE) among patients evaluated at a tertiary care Lupus Center for potential SLE

**Methods**—We identified patients first seen at the Brigham and Women's Hospital Lupus Center between January 1, 1992 and December 31, 2012 and thought to have potential SLE by a board certified rheumatologist. All had 1-3 SLE ACR criteria at initial visit and >2 follow-up visits 3 months apart. We reviewed medical records through May 15, 2013 for: SLE signs and symptoms, autoimmune serologies, prescriptions, and diagnoses by board certified rheumatologists. Bivariable analyses and multivariable logistic regression models were used to identify independent predictors of developing SLE.

**Results**—264 patients met inclusion criteria. At initial visit, mean age was 39.2 (SD 12.4) years, 94% were female and 67% white. Mean number of SLE ACR criteria was 2.7 (SD 1.0) and 88% were antinuclear antibody (ANA) positive at initial consultation. Mean follow-up time was 6.3 (SD 4.3) years and 67% were prescribed hydroxychloroquine in follow-up. At most recent visit, 56 (21%) had been diagnosed with SLE; 47 (18%) were thought not to have SLE; and 161 (61%) were still considered to have potential SLE. In multivariable regression models, oral ulcers (OR 2.40, 95% CI 1.03-5.58), anti-dsDNA (OR 2.59, 95% CI 1.25-5.35) and baseline proteinuria or cellular casts (OR 16.20, 95% CI 1.63-161.02) were independent predictors of developing SLE. The most common other final diagnoses included fibromyalgia, Sjögren's syndrome, mixed connective tissue disease and cutaneous lupus.

**Conclusion**—Among patients with potential SLE at initial consultation, 21% were diagnosed with definite SLE within 6.3 years. Oral ulcers, anti-dsDNA and proteinuria or cellular casts were independent predictors of developing definite SLE. A better means of accurately identifying those who will develop SLE among those presenting with potential disease is necessary.

### Keywords

systemic lupus erythematosus; prognosis; serology; presentation; manifestation; risk factor; diagnosis; incomplete lupus

## Introduction

Systemic lupus erythematosus (SLE) is a heterogeneous autoimmune disease with a diverse constellation of clinical features. As SLE can potentially lead to serious multi-system organ damage, early detection could have important implications for morbidity and management. However, due to the diverse manifestations of SLE and their evolution over time, it can be challenging to diagnose. Clinicians often use terms such as “possible lupus”, “incomplete lupus”, “latent lupus”, and “undifferentiated connective tissue disease” to describe patients who have features of SLE, but do not fulfill ACR classification criteria. Understanding which patient presentations are associated with the highest risk of developing into SLE would help in the development of studies regarding early treatment interventions, as well as provide both clinicians and patients with better risk assessment tools and inform clinical practice. Our aim was to identify factors associated with the evolution to SLE in a large cohort of patients thought by SLE-specialist rheumatologists to have “potential SLE” at initial consultation.

## Patients and Methods

### Study population

All patients seen in the Brigham and Women's Hospital (BWH) Lupus Center in Boston, Massachusetts for potential SLE since 1992 have been prospectively enrolled into the BWH Lupus Registry. Basic demographics, all American College of Rheumatology (ACR) criteria for the classification of SLE<sup>1, 2</sup>, all other presenting features of SLE, date of onset of first symptoms, date of SLE diagnosis, treating rheumatologist's name, and whether the diagnosis was thought to be definite SLE, potential SLE, or not SLE per the treating rheumatologist, have been collected in the Lupus Registry. From these data, we identified patients seen at the BWH Lupus Center who: (1) had an initial consultation between January 1, 1992 and December 31, 2012, (2) were thought to have potential SLE (but not definite) by their evaluating board certified rheumatologist, (3) had 1-3 ACR criteria for SLE classification at the initial consultation, and (4) had > 2 further visits each 3 months apart to our Lupus Center. The Partners Healthcare Institutional Review Board (IRB) approved of all aspects of this study.

### Data Collection

Patient data were retrieved from all electronic medical records from the first consultation through the last visit, on or before May 15, 2013. Clinical data collected from the initial consultation and all subsequent visits until study end included: the presence or absence of all ACR criteria for SLE<sup>1, 2</sup>, Raynaud's phenomenon, alopecia, weight loss, fever, headache, fatigue, vasculitis, thromboses, sicca symptoms, cutaneous and neurologic manifestations. We also compiled laboratory data, including presence or absence of antinuclear antibodies (ANA), anti-double stranded DNA (ds-DNA), anti-Ro (SSA), anti-La (SSB), anti-Sm, anticardiolipin antibodies (aCL), anti- $\beta$ 2 glycoprotein-1 antibodies, lupus anticoagulant, rheumatoid factor (RF), C3, C4 and CH50 complements, complete blood counts, and Coomb's tests. The course of illness, all medications prescribed, complications and deaths were also recorded. These medical record reviews were performed by one board-certified

rheumatologist (MA) and all cases in which the reviewer disagreed with the treating rheumatologist as to the final diagnosis were further reviewed by a second board-certified rheumatologist (KHC) for final diagnosis.

### Statistical Analysis

Patients were divided into three mutually exclusive groups according to their diagnoses at last follow-up: 1) “definite SLE”, defined as having received a diagnosis of SLE by the treating rheumatologist and the reviewing rheumatologist concurring; 2) still “potential SLE” if thought not conclusively, but potentially, to have SLE by either treating or reviewing rheumatologist, or both, and; 3) “not SLE” group, were not thought to have SLE per the treating or reviewing rheumatologist. Descriptive statistics and bivariable analyses, Fisher's exact tests for categorical variables and student's t-test for continuous variables, were used to compare the baseline characteristics of patients according to their final categorization. A multivariable logistic regression model including age, sex, race/ethnicity, calendar year, and the significant bivariable analysis factors, was used to identify independent predictors of developing definite SLE. All analyses were performed using software SAS Version SAS 9.3 and p value thresholds for interpreting significance were adjusted using a Bonferroni correction for multiple comparisons when examining multiple baseline clinical characteristics.

### Results

Within the BWH Lupus Registry, we identified 264 patients who were seen in initial consultation for potential SLE from 1992 to 2012 and met our inclusion criteria. (**Table 1**) Of these, 249 (94%) were female; the mean age at initial consultation was 39.2 ( $\pm$  12.4) years; the majority were white (67%); and the mean number of ACR criteria for classification of SLE was 2.7 ( $\pm$  1.0). The patients were evaluated by 32 different board certified attending rheumatologists. A positive ANA was found in 88.3% of these patients at the time of the initial consultation (before laboratories were performed for that visit). Over half (53%) had arthritis at the initial consultation, 17% had a positive anti-dsDNA antibody, 14% had a malar rash, 2% had proteinuria or urinary casts (per ACR classification criteria<sup>1, 2</sup>). None had biopsy-proven lupus nephritis. Only 1% had a discoid lupus rash at their initial consultation.

Mean follow-up was 6.3 (SD 4.6) years and the mean total number of visits per subject was 11.3 (SD 10.8). The mean time from the initial presentation to the next new symptom or laboratory/immunological event was 20 months (range 0.2-15 years). The most common subsequent clinical event to develop was a positive anti-dsDNA antibody (16 subjects). At the last follow-up visit, the mean number of ACR criteria for SLE among all the 264 patients had increased to 3.1 ( $\pm$ 1.4). At that time, 56 (21%) patients were classified as “definite SLE”, 161 (61%) still as “potential SLE”, and 47 (18%) as “not SLE”. (**Table 2**) Three patients were classified as having definite SLE with less than 4 ACR criteria: two had biopsy-proven lupus nephritis, as well as ANA and anti-dsDNA antibodies, and one had transverse myelitis, an ANA, anti-dsDNA antibodies and leukopenia. There were no differences in sex or race/ethnicity between the groups, but the patients who were thought to

not have SLE were slightly older, both at baseline and at the end of follow-up than those in the other two groups. There were two deaths in the definite SLE group, one due to end-stage liver disease and one from lung cancer; nine deaths in the potential SLE group: one from ovarian cancer, one from colorectal cancer, four due to lung cancer, one from pulmonary hypertension, one due to end-stage renal disease (not due to SLE), and one from unknown causes. There was one death among those thought not to have SLE due an unknown cause.

Arthritis at the initial consultation was more common in the definite SLE group (71%), compared to the potential SLE (57%) and not SLE groups (36%). (**Table 3**) Anti-dsDNA was also significantly more prevalent at the initial visit among the definite SLE group (43%), compared to those classified as still having potential SLE (16.2%) or not SLE (9%). At the initial visit, anti-Ro was also more common in those who went on to develop definite SLE (29%) compared to those who were still thought to have potential SLE at the end of follow-up (16%). In multivariable logistic regression including the significant clinical variables in table 3 as well as age, sex, race/ethnicity and calendar year, only oral ulcers (OR 2.40, 95% CI 1.03-5.58), anti-dsDNA (OR 2.59, 95% CI 1.25-5.35) and persistent proteinuria or urinary cellular casts (OR 16.20, 95% CI 1.63-161.02) were found to be independent baseline predictors of development of definite SLE.

A large proportion of patients (67%) were prescribed hydroxychloroquine in follow-up regardless of their final diagnoses. It was prescribed to 80% of patients with final definite SLE, but also to 65% of patients still thought to potentially have SLE and 62% of patients ultimately thought not to have SLE. Oral corticosteroids were prescribed at some point during follow-up to 38% of patients in the definite SLE group, 35% of those thought to still potentially have SLE, and 28% of those ultimately thought not to have SLE (**Table 4**).

Among the 47 patients who were categorized as “not SLE” at the end of follow-up, 19% were diagnosed with fibromyalgia, 14% with autoimmune thyroid disease, 8% with mixed connective tissue disease (MCTD), 6% with rheumatoid arthritis and 6% with cutaneous lupus (**Figure 1**). Thirteen percent were prescribed methotrexate.

## Discussion

We identified 264 patients who were seen in initial consultation and subsequently followed at our Lupus Center over a twenty year period for “potential SLE. None had a definite diagnosis of SLE at their first consultation, yet all had features that suggested that they may evolve into SLE. Eighty-eight percent of these patients had a positive ANA upon referral. The majority of patients (61%) were still thought to have potential SLE at final follow up, a mean 6.3 years later; 21% of patients had progressed to definite SLE and 18% were eventually thought not to have SLE. We found that patients who had proteinuria and urinary cellular casts, oral ulcers or an anti-dsDNA at the first consultation were at highest risk of being later diagnosed with SLE. A large proportion of the entire group was also prescribed hydroxychloroquine. As this is a retrospective review, we do not know whether taking hydroxychloroquine impacted whether patients developed SLE. In a past retrospective cohort study of 130 military recruits with data prior to SLE diagnosis, patients who received either hydroxychloroquine or prednisone developed SLE more slowly than those who did

not.<sup>3</sup> Thus, it is possible that receiving hydroxychloroquine could have retarded the development of SLE and, as this was not a randomized trial, we do not know the natural history of untreated potential SLE.

Previous studies have investigated the evolution of SLE from “incomplete lupus” (fewer than four ACR criteria) or undifferentiated connective tissue disease (UCTD, patients with clinical, laboratory, and serologic features characteristic of more than one rheumatic disease) by identifying clinical and serological predictors of the development of SLE<sup>5-10</sup>. For example, Vilá LM and colleagues followed a group of 87 patients with “incomplete lupus” for a mean of 2.2 years and found that only 9% evolved to SLE. In that study, malar rash, oral ulcers, anti-dsDNA and decreased C4 were associated with evolution to SLE<sup>2</sup>. Stahl Hallengren identified 28 patients with “incomplete SLE” in Northern Sweden and, after 10 years, 57% had developed definite SLE. Malar rash and anticardiolipin antibodies were predictors of developing complete SLE in that Swedish cohort<sup>11</sup>. In contrast, in another study of 84 patients with UCTD in which 22 developed SLE after at least five years of follow-up, only anticardiolipin antibodies were found to predict development of SLE and another six patients developed other forms of connective tissue disease<sup>10</sup>. Other studies have also identified serositis, alopecia, and anti-dsDNA antibodies as predictors of evolution to SLE<sup>6, 12</sup>. Our study adds to these past studies by confirming that oral ulcers, renal manifestations and anti-dsDNA were highly predictive of the development of SLE, but antiphospholipid antibodies were not predictive of SLE in our cohort.

Our study underscores the point that the term “incomplete lupus” is often misleading, as 18 % of the patients received a final diagnosis other than SLE and 56% remained undiagnosed after a substantial follow-up period. Thus, we prefer the term “potential SLE” to describe those patients who after initial evaluation by a rheumatologist are thought to potentially have or be developing SLE. The ability to definitively diagnose these patients with or without SLE as early as possible has implications for both potential early therapies and health care cost containment. If those patients who are not at risk for ultimately developing SLE could be reassured of that at the time of their initial consultation, many expensive follow-up visits and laboratory testing could be circumvented. It is reassuring that none of the deaths that occurred among this entire cohort of 264 patients during follow-up was attributable to SLE.

The strengths of our study are that it utilizes a large study population at a single large academic center with a relatively long follow-up period (more than six years), and clinical data were well documented and prospectively recorded in the electronic medical records. The limitations of our study include its retrospective data collection and the observational nature of the data in which patients were not assigned to medications and had unequal follow-up. There was also variation in rheumatologist practice style in terms of follow-up, laboratory ordering, and treatment.

In summary, in this cohort of 264 patients seen for potential SLE, approximately one fifth were diagnosed with definite SLE that fulfilled ACR classification criteria within a mean of 6.3 years of follow-up. Persistent proteinuria and urinary cellular casts, anti-dsDNA, and oral ulcers at the time of the initial consultation were predictive of the development of SLE in follow-up. However, over 60% of this cohort had features of SLE and were still being

followed for potential SLE at the end of follow-up. An improved understanding of the biological and clinical predictors of disease progression in this specific group of patients—i.e. those that go on to develop SLE but do not appear to have the disease at presentation—would be a valuable contribution, enabling an earlier diagnosis in this patient population, although such studies are just beginning<sup>13, 14</sup>. Furthermore, a better means for earlier identification of those who are not likely to progress to develop SLE would be useful clinically and potentially cost saving for patients who have multiple visits and even take potentially toxic medications that may not be indicated given a low risk of developing SLE.

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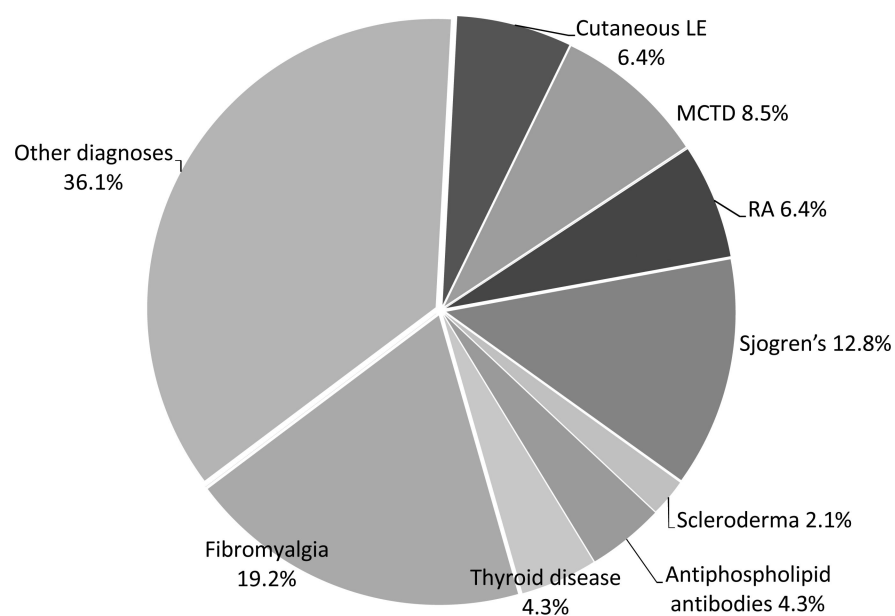
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**Figure 1.**  
Prevalence of Final Non-SLE Diagnoses among the 47 Patients determined “Not SLE” at end of Follow-up



**Table 1**

Demographics and Clinical Characteristics of 264 Patients seen in Consultation for “Potential SLE” between 1992-2012

Characteristics	N (%)
Age, mean (SD) years	39.2 (12)
Mean no. of ACR criteria (SD)	2.7 (1)
Female, (%)	249 (94)
Family History of SLE, (%)	26 (10)
Race/Ethnicity	
White	178 (67)
Black	29 (11)
Asian	15(6)
Hispanic	17(6)
Others	25 (10)

**Table 2**

Demographic and Clinical Characteristics at Latest Follow-up of 264 Patients seen in Consultation for “Potential SLE” between 1992-2012

	Definite SLE N= 56	Potential SLE N= 161	p value *	Not SLE N= 47	p value **
Mean age at first visit (SD), years	36.9 (11)	39.3 (13)	0.22	41.5 (13)	0.05
Mean follow up (SD), years	6.4 (4)	5.9 (5)	0.49	7.6 (6)	0.19
Mean age at follow up (SD), years	46.5 (11)	49.5 (14)	0.15	53.2 (13)	<b>0.007</b>
Deaths in follow-up (%)	2 (4)	9 (6)	0.73	1 (2)	1.00

\* Definite SLE vs. Potential SLE

\*\* Definite SLE vs. Not SLE. t -tests for continuous and Fisher's exact for categorical variables

**Table 3**

Baseline Clinical Characteristics of 264 Patients seen in Consultation for “Potential SLE” between 1992-2012, by Final Diagnosis at End of Follow-up

	Definite SLE n= 56 (%)	Potential SLE n= 161 (%)	p value *	Not SLE (n=47) %	p value **
Malar Rash	14	11	0.63	13	1.00
Discoid Rash	2	1.	1.00	0	1.00
Photosensitivity	21	22	1.00	21	1.00
Oral Ulcers	20	11	0.12	9	0.16
Arthritis	71	57	0.08	36	< 0.001
Serositis	21	13	0.14	15	0.45
Renal Disease ***	11	1	0.001	0	--
Hematologic Involvement	45	30	0.07	32	0.22
Neurologic Involvement	4	4	1.00	11	0.24
ANA ****	100	98	0.57	79	<0.001
Anti-dsDNA ****	43	16	<0.001	9	<0.001
Anti-Sm ****	11	3	0.02	4	0.28
Anticardiolipin antibodies ****	16	14	0.83	15	1.00
Lupus anticoagulant ****	2	4	0.59	4	0.59
Beta2-glycoprotein1 antibodies ****	0	2	0.57	2	0.46
Rheumatoid factor ****	2	9	0.18	9	0.18
Anti-Ro ****	29	16	0.04	19	0.35
Anti-La ****	11	8	0.58	11	1.00
Alopecia	25	21	0.58	19	0.64
Low Complement ****	38	19	0.006	28	0.30
Fevers	9	10	1.00	6	0.72
Headache	21	12	0.04	19	0.81
Fatigue	54	42	0.16	38	0.16
Vasculitis	2	3	1.00	6	0.33
Thrombosis	9	4	0.19	6	0.72
Miscarriages	5	5	1.00	6	1.00
Sicca symptoms	14	12	0.64	17	0.78

\* and \*\* thresholds for interpreting significance after Bonferroni correction for multiple comparisons= < 0.0019

\* definite SLE vs. possible SLE

\*\* definite SLE vs. not SLE. Fisher's exact tests

\*\*\* Renal disease: persistent proteinuria or cellular casts per ACR criteria

\*\*\*\* All laboratories upon referral and prior to performance of BWH Lupus Center laboratories

**Table 4**

Medications Received during Follow-up by Potential SLE Patients

Medication	All Patients n= 264 (%)	Diagnosis at Most Recent Follow-up				
		Definite SLE n= 56, %	Potential SLE n= 161, %	* p	Not SLE n= 47, %	** p
Hydroxychloroquine	67.4	80.4	64.6	<b>0.03</b>	61.7	<b>0.04</b>
Other Antimalarial	2.6	5.4	0.6	<b>0.05</b>	6.4	1.00
Oral Corticosteroids	38.3	57.1	34.8	<b>0.004</b>	27.7	<b>0.003</b>
IV Corticosteroids	1.5	3.6	0.6	0.16	2.1	1.00
Azathioprine	3.4	7.1	1.8	0.07	4.3	0.68
Mycophenolate Mofetil	4.6	12.5	2.5	<b>0.007</b>	3.1	0.06
Cyclophosphamide	1.5	5.4	0.6	<b>0.05</b>	0	0.24
Methotrexate	11.4	16.1	9.3	0.21	12.8	0.77
Sulfasalazine	6.1	3.6	5.6	0.73	10.6	0.24
Rituximab	0.4	0	0.6	1.00	0	1.00
Other Biologics	3.0	1.8	3.1	1.00	4.3	0.59

\* definite SLE vs. possible SLE

\*\* definite SLE vs. not SLE. Fisher's exact tests