Predictors of Carotid Atherosclerosis in Systemic Lupus Erythematosus

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ABSTRACT. ***Objective***. Patients with systemic lupus erythematosus (SLE) are at increased risk for cardiovascular and cerebrovascular events, even after adjustment for traditional risk factors. We examined the association of traditional risk factors, novel markers of cardiovascular disease (C-reactive protein, homocysteine, lipoprotein(a), plasminogen activator inhibitor-1, fibrinogen), and markers indicative of SLE activity (including C3, C4, anti-dsDNA, and prednisone use) with the presence of significant plaque on carotid duplex imaging.

Methods. Six hundred five patients with SLE enrolled in the Hopkins Lupus Cohort Study (92% female, 38% African-American) underwent carotid duplex testing. Prospectively gathered clinical, laboratory, and serologic data from their quarterly followup visits in the Hopkins Lupus Cohort were used in the analyses. For predictors that varied over time, such as cholesterol, the mean values during cohort participation were calculated for the analysis. Informed consent was obtained from all patients.

Results. The presence of carotid plaque was strongly associated with age, ranging from 1% among those less than 30 years of age to 61% among those 60 years or older. After adjusting for age, there were moderate or strong associations of carotid plaque with male gender (age-adjusted risk 25% vs 13%; p = 0.051), hypertension (age-adjusted risk 18% vs 8%; p = 0.0001), diabetes mellitus (age-adjusted risk 19% vs 13%; p = 0.075), C3 > 120 mg/dl (age-adjusted risk 18% vs 11% and 14% for normal and low C3, respectively; p = 0.046), serum creatinine > 1.3 (age-adjusted risk 32% vs 13%; p = 0.039), and mean systolic blood pressure > 140 (age-adjusted risk 23% vs 13%; p = 0.028). There was no strong evidence of an association between plaque and SLE disease activity (age-adjusted risk 14% among those with adjusted mean SLEDAI > 3 vs 14% among those with lower SLEDAI) or with time since SLE diagnosis (age-adjusted risk 12%, 14%, and 16% among those with SLE for < 2, 2–8, and > 8 years, respectively; p = 0.49).

Conclusion. Traditional cardiovascular risk factors were associated with carotid plaque in SLE. However, SLE disease activity and duration of SLE are not strongly associated with carotid plaque. A "lupus factor" separate from traditional risk factors remains unidentified. (First Release Oct 1 2006; J Rheumatol 2006;33:2458–63)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS CAROTID PLAQUE RISK FACTORS

The increased prevalence of premature atherosclerosis in patients with systemic lupus erythematosus (SLE) is well established. This was first documented in an autopsy series performed in the 1970s that detected moderate or severe atherosclerosis in up to 54% of patients, independent of the cause of death[1]. As therapeutic interventions have improved, leading to increased life expectancy in patients with SLE, this complication is becoming an important factor in disease-related morbidity. Manzi, *et al* found that, in women 35 to 44 years of age, those with SLE were 50 times more likely to have an acute myocardial infarction than age and sex matched subjects from the Framingham cohort[2]. Esdaile, *et al* calculated the probability of cardiovascular events in SLE patients using the Framingham model. SLE patients were found to have strikingly increased relative risks (RR) of nonfatal myocardial infarction (RR = 10.1), death from cardiovascular disease (RR = 17), and stroke (RR = 7.9)[3].

Traditional cardiovascular risk factors, including hyperlipidemia, hypertension, and tobacco use, are frequent in patients with SLE[4]. These traditional cardiovascular risk factors are also associated with coronary artery disease in SLE[5]. Bruce, *et al* found that detection and treatment of these well established risk factors are suboptimal, suggesting that the lack or inadequacy of therapeutic interventions could be an important contributing factor to cardiovascular disease risk in patients with SLE[6]. In addition, SLE patients with coronary artery disease have a lower mean number of individual traditional risk factors when compared to non-lupus patients with coronary artery disease[7]. The recent paradigm shift to the recognition of atherosclerosis as an inflammatory disease leads to an obvious

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question: Is the systemic inflammation associated with lupus activity an instigating or accelerating factor (or both) in atherosclerosis in SLE?

Prior studies have documented a strong association between carotid plaque and coronary artery disease[8]. The Hopkins Lupus Cohort is a prospective study of lupus outcomes in which patients are seen on a quarterly basis. Our objective was to examine novel markers of atherosclerosis and markers of SLE activity, in addition to traditional risk factors, for correlation with the presence of carotid plaque.

MATERIALS AND METHODS

Patients. The Hopkins Lupus Cohort of patients with SLE is seen quarterly at Johns Hopkins University outpatient clinic. Routine data assessed at every cohort visit include weight, blood pressure, erythrocyte sedimentation rate (ESR), creatinine, serum C3, serum C4, anti-dsDNA, physician's estimate of activity, and SLE Disease Activity Index (SLEDAI).

For our substudy, consecutive active members of the cohort were asked to undergo carotid duplex testing to assess the presence of carotid plaque for research purposes. Informed consent was obtained from 605 patients.

Carotid plaque assessments. Carotid duplex was performed using high resolution linear transducers (5–10 MHz; Acuson 128XP, Hewlett Packard Image Point or ATL HDI 3000) in the Department of Radiology, Johns Hopkins Hospital. Images were acquired of the distal common carotid arteries (CCA), carotid bulb, and proximal internal carotid arteries (ICA) in the sagittal plane. Intima thickness was measured at the near and far walls of the distal CCA, and Doppler spectrum tracings were taken in the first 2 cm of the proximal ICA. Flow velocities of the CCA and ICA were also obtained. If atherosclerotic plaque was identified, transverse images and measurements of plaque were obtained.

Definitions of independent variables. High weight was defined as being in the upper quartile for gender (> 154 lb in females, > 186 lb in males). Hypertension was defined as a systolic blood pressure > 140 and diastolic blood pressure > 90 mm Hg, or the use of antihypertensive medications. Diabetes mellitus was defined as the use of insulin or oral hypoglycemic drugs. Hydroxychloroquine and prednisone use were recorded at each visit.

Clinical characteristics of the study sample. The majority (91%) of the 605 patients in the study were female. The patients were 58% Caucasian, 39% African-American, with mean age 46.5 years (range 18 to 94, with about half the sample under 45). Sixty-two percent had malar rash, 25% discoid rash, 59% photosensitivity, 47% mouth or nasal ulcers, 56% alopecia, 17% vasculitis, 80% arthritis, 47% pleurisy, 25% pericarditis, 47% proteinuria, 19% nephrotic syndrome, 32% hematuria, 18% renal insufficiency, 5% renal failure, 9% seizures, 3% psychosis, 8% encephalopathy, 11% hemolytic anemia, 52% leukopenia, 48% lymphopenia, 25% lupus anticoagulant, 37% anticardiolipin, and 82% high ESR. In terms of serologic tests, 62% had anti-dsDNA, 28% anti-Ro, 10% anti-La, 60% low C3, 53% low C4, 25% anti-RNP, and 15% anti-Sm. Twenty-three percent had had a thrombotic event, 5% a stroke, and 4% a myocardial infarction. At the time of plaque assessment, the mean time since SLE diagnosis was 6.5 years: about one-third had had SLE for less than 2 years and one-third for more than 8 years. The mean time since entering the cohort was 3.8 years: some patients had participated more than 12 years, but almost half (47%) for less than one year. About half (48%) had hypertension, 7% had diabetes mellitus, and 43% had a history of smoking.

Activity measures. Disease activity measures (Physician's Global Assessment, SLEDAI) were completed prospectively during cohort followup. Anti-dsDNA was measured by Crithidia.

Damage measure. The Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index was updated at every cohort visit[9].

Risk factors for cardiovascular disease. Fasting lipid profile, fibrinogen, C-reactive protein (CRP), lipoprotein(a), homocysteine, and glucose were measured in the clinical laboratory. Lupus anticoagulant was measured by dilute Russell viper venom time, followed by mixing studies and a confirmatory study. Anticardiolipin IgG, IgM, and IgA were measured by ELISA.

Statistical methods. To assess the association between various patient characteristics and the presence of plaque, we defined subgroups based on the patient characteristics and then compared the proportion of patients with plaque in these subgroups. To assess the degree to which these proportions were statistically significantly different, we calculated p values based on Pearson's chi-square test. In addition, since age was a strong predictor of the presence of plaque, and age was also strongly associated with many of the predictors, we calculated age-adjusted proportions with plaque, and age-adjusted p values. The age-adjusted proportions with plaque were calculated using direct age-standardization, standardizing to the age-distribution of the study sample. The age-adjusted p values were calculated using logistic regression, including dummy variables for the age strata. Cutpoints for the definition of subgroups based on continuous measures were generally chosen to correspond to ranges considered clinically normal. However, some exceptions were made when this resulted in small numbers of subjects in some subgroups. To classify subjects with respect to the subgroups, mean values of time-varying predictors were calculated using only those cohort visits prior to the measurement of plaque. To classify the subjects with respect to the extent of their SLE activity, their adjusted mean SLEDAI prior to the plaque measurement was calculated using the method of Ibanez, *et al*[10]. The number of measurements used to calculate these means varied from 1 to 126 (depending on number of visits by a patient), but the majority were based on fewer than 10.

RESULTS

Univariate associations between factors associated with the presence of plaque. Tables 1 and 2 show the degree to which various patient characteristics and clinical markers are associated with presence of plaque. The variable with the strongest association with plaque was found to be age: only 1/112 (1%) of those under 30 had plaque, whereas 25/41 (61%) of those over 60 years of age had evidence of plaque. Other patient characteristics associated with plaque in the univariate analysis included gender, history of smoking, family history, and diagnoses of hypertension or diabetes mellitus (Table 1). The time elapsed since diagnosis of SLE was not strongly associated with plaque. Considering the clinical markers (Table 2), higher rates of plaque were found among those with left ventricular hypertrophy, high levels of total cholesterol, glucose, homocysteine, serum C3, serum C4, creatinine, and high blood pressure (Table 2).

Age-adjusted associations between variables and presence of plaque. Because age is so strongly related to plaque and is also related to many of the other variables, the univariate associations for many variables are likely to be confounded by age. Tables 1 and 2 show the degree of association between various variables and plaque after adjusting for age: the only variables that remained strongly associated with plaque were diagnosis of hypertension, high serum C3 level, elevated creatinine, and high systolic blood pressure.

Associations between variables and presence of plaque based on a multivariable model. We fit a multivariable logistic regression model to assess the association between variables and presence of plaque, while controlling for other variables

Table 1. Association between various patient characteristics and presence of plaque in patients with SLE.

Variable	Proportion with Plaque (%)	p value*	Age Adjusted with Plaque**, %	Age Adjusted p value+
Total	85/605 (14)			
Age group				
< 30	1/112 (1)	0.001		
30–39	10/187 (5)			
40–49	20/175 (11)			
50–59	29/90 (32)			
60+	25/41 (61)			
Ethnicity				
Black	34/234 (15)	0.46	15	0.89
White	50/350 (14)		14	
Other	1/21 (5)			
Gender				
Male	13/52 (25)	0.017	24	0.051
Female	72/553 (13)		13	
Years since SLE diagnosis				
< 2 yrs	19/164 (12)	0.33	12	0.49
2–8 yrs	21/175 (12)		14	
8+ yrs	26/156 (17)		16	
Current smoking				
Yes	19/107 (18)	0.22	18	0.14
No	65/491 (13)		12	
History of smoking				
Yes	49/254 (19)	0.001	16	0.093
No	35/347 (11)		13	
Family history of cardiovascular disease				
Yes	10/31 (32)	0.005	21	0.13
No	71/516 (14)		14	
Hypertension				
Yes	68/288 (24)	0.001	18	0.0001
No	16/312 (5)		8	
Weight				
High	49/297 (17)	0.074	15	0.63
Low	33/290 (11)		13	
Diabetes mellitus				
Yes	15/45 (33)	0.001	19	0.075
No	70/557 (13)		13	
Plaquenil therapy	38/242 (16)	0.30	15	0.59
None during cohort	46/362 (13)		13	
Prednisone therapy	24/155 (15)	0.51	13	0.63
None during cohort	60/449 (13)		14	

* Based on Pearson's chi square statistic. ** Directly standardized to the age-distribution of the study sample.
+ Based on a logistic regression model controlling for the age groups indicated in the table.

in the model. In this model we initially only included variables that were associated with plaque based on the age-adjusted analysis, although we eliminated some redundant variables (e.g., we did not include a diagnosis of both hypertension and systolic blood pressure). The results are shown in Table 3. The strongest predictor continued to be age ($p < 0.0001$ for overall effect of age). It can be seen that after controlling for other variables in the model, high levels of serum C3 are still associated with a higher odds of plaque (OR = 1.9), although this association is not statistically significant by the traditional criterion ($p = 0.052$). Additional models were fit adding all the other clinical markers to this model, one at a time, and none were significantly associated with plaque at the 0.05 level.

SLICC/ACR Damage Index. Patients whose current SLICC/ACR Damage Index score was 3 points or higher were significantly more likely to have carotid plaque, even after age adjustment (Table 4).

Table 2. Association between clinical markers and presence of plaque.

Variable	Proportion (%) with Plaque	p value*	Age Adjusted % with Plaque**	Age Adjusted p value+
Left ventricular hypertrophy				
Yes	15/56 (27)	0.021	19	0.28
No	55/377 (15)		15	
CRP, mg/dl				
< 0.5	30/256 (12)	0.27	14	0.81
≥ 0.5	26/169 (15)		14	
Fibrinogen, mg/dl				
< 450	49/365 (13)	0.56	14	0.74
≥ 450	7/65 (11)		12	
Mean total cholesterol, mg/dl				
≤ 200	30/328 (9)	0.001	12	0.15
> 200	51/259 (20)		16	
HDL, mg/dl				
< 35	1/22 (5)	0.35	NA#	0.34
35–96	52/376 (14)		15	
> 96	3/15 (20)		11	
LDL, mg/dl				
< 57	4/18 (22)	0.36	19	0.65
57–130	36/298 (12)		14	
> 130	15/96 (16)		15	
Glucose, mg/dl				
< /100	40/355 (11)	0.010	13	0.074
> 100	18/82 (22)		19	
Homocysteine, mg/dl				
≤ 9	18/197 (9)	0.021	13	0.25
> 9	38/227 (17)		16	
Lipoprotein (a), mg/dl				
≤ 30	37/293 (13)	0.48	14	0.57
> 30	20/132 (15)		16	
Anticardiolipin, mean during cohort				
< 1.0	8/44 (18)	0.26	19	0.41
≥ 1.0	15/130 (12)		12	
C3, mean during cohort, mg/dl				
< 85	17/154 (11)	0.015	14	0.046
85–120	33/290 (11)		11	
≥ 120	32/156 (21)		18	
C4, mean during cohort, mg/dl				
< 15	13/158 (8)	0.002	10	0.16
15–26	34/277 (12)		14	
≥ 26	35/165 (21)		16	
Creatinine, mean, mg/dl				
< 0.6	2/33 (6)	0.019	13	0.039
0.6–1.3	70/523 (13)		13	
> 1.3	12/45 (27)		32	
Diastolic BP, mean, mmHg				
< 90	73/555 (13)	0.024	14	0.20
≥ 90	11/43 (26)		27	
Systolic BP, mean, mmHg				
< 140	53/501 (11)	0.001	13	0.028
≥ 140	31/97 (32)		23	
Anti-dsDNA positive				
Never	45/303 (15)	0.40	13	0.84
Once or more	37/296 (13)		14	
PGA, mean during cohort				
< 1	57/428 (13)	0.50	13	0.32
≥ 1	27/175 (15)		16	
SLEDAI, adj. mean during cohort				
< 3	52/327 (15)	0.12	14	0.90
≥ 3	32/277 (12)		14	
RVVT, mean during cohort				
< 37	22/157 (14)	0.53	13	0.67
> /37	2/22 (9)		NA#	

* Based on Pearson's chi square statistic. ** Directly standardized to the age-distribution of the study sample. + Based on a logistic regression model controlling for the age groups indicated in the table. # Not calculated due to no observations in some age groups. BP: blood pressure; PGA: Physician's Global Assessment; SLEDAI: SLE Disease Activity Index; RVVT: Russell viper venom time.

Table 3. Associations between various factors and presence of plaque based on a multivariable logistic regression model.

Variable	Odds ratio (95% CI)	p value
Age Group, yrs		
0–30	0.01 (0.001; 0.09)	0.0001
30–39	0.05 (0.02; 0.15)	0.0001
40–49	0.12 (0.05; 0.27)	0.0001
50–59	0.40 (0.17; 0.94)	0.036
60+	1.00 (reference group)	
Gender		
Male	1.7 (0.7; 4.4)	0.25
Female	1.0 (reference group)	
Family History		
Yes	1.6 (0.6; 4.4)	0.35
No	1.0 (reference group)	
Hypertension		
Yes	2.6 (1.4; 5.1)	0.0044
No	1.0 (reference group)	
Diabetes mellitus		
Yes	1.6 (0.7; 3.8)	0.26
No	1.0 (reference group)	
History of smoking		
Yes	1.5 (0.8; 2.6)	0.20
No	(reference group)	
Creatinine, mg/dl		
< 0.6	0.9 (0.2; 5.8)	0.94
0.6–1.3	1.0 (reference group)	
> 1.3	2.1 (0.8; 5.5)	0.13
C3, mg/dl		
< 85	1.4 (0.8; 2.9)	0.38
85–120	1.0 (reference group)	
> 120	1.9 (1.0; 3.7)	0.052

DISCUSSION

Traditional cardiovascular risk factors are important in the pathogenesis of atherosclerosis in SLE[5]. Some of these "traditional" factors (including hypertension or hyperlipidemia) may result from or are exacerbated by SLE and by therapeutic interventions (e.g., prednisone treatment). The identified factors amenable to intervention include smoking, hypertension, hypercholesterolemia, homocysteine, and hyperglycemia[5,11,12]. However, patients with SLE have an increased incidence of atherosclerosis or clinically detected coronary artery disease beyond that explained by traditional cardiovascular risk factors[3,7,13]. A continued challenge is to identify a marker of the "lupus factor."

The lack of association between the presence of carotid plaque and typical measures of lupus activity (low serum C3, low serum C4, high anti-dsDNA, clinical indices) in our study does not discount the concept of inflammation as a key component of atheroma formation. By our current understanding, atherosclerosis is a multifactorial process, with genetic and environmental influences, and a highly heterogeneous expression. The association of plaque with increased (rather than low) complement levels suggests that markers of the acute phase reaction may be more useful in detection and monitoring processes related to endothelial injury and atherogenesis

Table 4. Association between SLICC Damage Index and presence of carotid plaque in patients with SLE.

Variable	Proportion (%) with Plaque	p value*	Age Adjusted % with Plaque**	Age Adjusted p value+
Damage Index				
0–2	16/289 (5)	< 0.0001	9	0.0002
3+	69/312 (22)		18	

* Based on Pearson's chi square statistic. ** Directly standardized to the age-distribution of the study sample. + Based on a logistic regression model controlling for the age groups indicated in the table. SLICC: Systemic Lupus International Collaborating Clinics.

in patients with SLE. However, standard markers of the acute phase reaction (ESR, CRP) have not consistently demonstrated predictive value or association with atherosclerosis when various SLE cohort studies are compared. However, more sensitive markers of systemic inflammation are emerging for use in atherosclerosis prediction. High sensitivity CRP, which was not available in the cohort database, is rapidly gaining acceptance as an inflammatory predictor of atherosclerosis in the general population[14]. Moreover, increasing evidence suggests that high sensitivity CRP is not only a risk marker but also a risk factor in atherogenesis[15].

The patients with SLE that may be at greatest risk for atherosclerosis based on our data (those with a high serum C3 or hypertension) might not be identified by rheumatologists as having the "worst" or most active lupus. This reinforces findings from our earlier study, in which SLE patients who needed high-dose prednisone or pulse intravenous methylprednisolone for organ-threatening or life-threatening active disease were not found to have an increased relative risk of atherosclerosis[16]. Additionally, in their recent case-control study, Roman, *et al*[17] found that patients with carotid plaque had received or were currently receiving less immunosuppressive therapy (including corticosteroids cyclophosphamide, and antimalarials) than patients without plaque.

Although this observation initially appears counterintuitive, other studies lend support to our finding of elevated serum C3 as a predictor of atherosclerotic disease and associated events. In the general population, elevated serum C3 is an independent predictor of risk of myocardial infarction in men without previous ischemic events[18]. Manger, *et al* also found that elevated C3 levels were predictive of coronary artery calcification and were more commonly found to be associated with symptomatic coronary heart disease in women with SLE[19]. More recently, an association between elevated serum C3 and aortic stiffness (a predictor of cardiovascular events and mortality) was identified in women with SLE in the Pittsburgh cohort[20]. Although the role of C3 in atherogenesis remains unclear, there is evidence that, in the general population, C3 levels correlate with waist circumference and postprandial lipemia, suggesting a possible mechanism related to more traditional risk factors[21].

It is also possible that these findings reflect an increased risk of coronary artery disease in SLE patients with persistent low level disease activity ("grumbling disease"), whose disease, because of absence of overt severe manifestations, may be treated less aggressively (i.e., fewer agents, or with lower doses or shorter duration of therapy). Perhaps chronicity, rather than severity, of systemic inflammation has the greatest impact on atherogenesis. Further investigation is necessary to better elucidate this relationship. This "disconnect" between the clinical assessment of lupus severity and the risk of atherosclerosis remains an enigma.

There are some limitations to our study that should be considered in interpreting our results. First, given our sample size and the strong association between plaque and age, our power was somewhat limited to identify additional risk factors for plaque. Therefore, although we did not observe a strong association between many variables and plaque, the data do not generally rule out the possibility of important associations. Second, it should be noted that many subjects were not in the cohort for the entire time since their diagnosis with SLE. Thus, the mean level of activity, complement, and other variables observed during cohort participation might not accurately represent the mean levels since time of diagnosis of SLE. This could further reduce our power to find associations. Finally, it should be remembered that carotid plaque can be viewed as a surrogate for important clinical events such as stroke and myocardial infarctions. Surrogates can be useful in clinical research, but interpretation requires caution[22] because associations with a surrogate do not always result in a correlation with clinical events. Our results should be confirmed in future studies that use clinical events as endpoints.

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