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The ratio of erythrocyte sedimentation rate to C-reactive protein is useful in distinguishing infection from flare in systemic lupus erythematosus patients presenting with fever

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Abstract

Background—Both C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) can be elevated in systemic lupus erythematosus (SLE) flare and infection, and are therefore of limited utility for distinguishing between the two conditions in febrile SLE patients.

Methods—A medical records review of hospitalizations (1997–2006) from SLE patients in the Michigan Lupus Cohort was performed. Eligible hospitalizations were those where patients presented with a temperature of $>100.3^{\circ}$ F or with subjective fevers as a presenting complaint at admission. Detailed demographic, clinical and laboratory data were collected. Multivariable logistic regression was used to examine the associations between ESR and CRP and the outcome of flare versus infection, adjusted for confounders.

Results—Among 557 SLE patients screened, there were 53 eligible hospitalizations (28 flares and 25 infections). Each unit increase in the ratio of ESR:CRP was associated with a 17% increase in the odds of fever being attributable to SLE flare compared to infection (OR 1.17, 95% CI 1.04, 1.31; $p=0.009$), when adjusted for white blood cell count, SLE duration, sex, race, and age. ESR and CRP were not individually associated with flare versus infection when modeled with their ratio.

Conclusions—The ratio of ESR:CRP may provide diagnostic value beyond individual ESR and CRP levels in distinguishing flare versus infection in SLE patients presenting with fever.

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INTRODUCTION

In patients with systemic lupus erythematosus (SLE) who develop fever, it is often difficult to distinguish a lupus disease flare from an infectious process. Appropriate treatment of lupus flare is often delayed while an infectious work-up is undertaken, which may include waiting days for culture results. Since presumptive treatment of SLE flares with immunosuppressive medications, including high dose glucocorticoids, can be dangerous in the setting of an infection, aggressive immunosuppression is usually postponed until an infectious process is excluded. Clinical or laboratory information that aid in distinguishing flare versus infection in these situations would be of significant utility.

C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), both non-specific markers of systemic inflammation, are potentially useful biomarkers in this frequently encountered clinical scenario. Both CRP and ESR can be elevated in inflammation due to autoimmune disease, infection or malignancy. When compared to patients with rheumatoid arthritis, SLE patients have been shown to have a higher likelihood of elevations of ESR than CRP (1), but ESR rises with both lupus activity and infection, making it too non-specific to distinguish between lupus flare and infection (2). Whereas ESR elevations are strongly associated with disease exacerbations in SLE (3), CRP levels do not tend to correlate with other markers of disease activity such as anti-double stranded DNA antibodies and complement levels (4). However, CRP values of >6.0 mg/dl in SLE patients have been associated with infectious processes in several studies (5–7) and higher CRP levels have been observed in SLE infection compared to SLE flare without infection (8,9). It has also been suggested that SLE flares of serositis (pleuritis, pericarditis, pneumonitis) or flares involving nephritis or myositis present with a significantly higher CRP than other types of SLE flares (10), further complicating the interpretive clinical picture.

We conducted this retrospective study to further clarify the utility of CRP and ESR, alone or in combination, in distinguishing between flare and infection in SLE patients presenting with fever.

METHODS

Study population

Electronic records of 557 patients in the Michigan Lupus Cohort were reviewed for admission events to the University of Michigan Hospital with fever during years 1997–2006. This setting is a large, university teaching hospital with a multispecialty lupus clinic. The Michigan Lupus Cohort is comprised of patients meeting the American College of Rheumatology (ACR) criteria for SLE (11,12). This research was approved by the University of Michigan Institutional Review Board, and written informed consent was obtained.

Eligibility criteria—Inclusion criteria were as follows: hospitalized patients with SLE fulfilling 4 ACR criteria, with a temperature of >100.3° Fahrenheit on admission, or subjective fevers as a presenting complaint. Standard practice at our institution is to measure temperature using digital oral thermometers. Exclusion criteria were: patients not meeting

ACR criteria for SLE, patients with chart documentation of both SLE flare and infection during their hospital stay, missing ESR and CRP data from the admission, presence of underlying malignancy, known chronic infection (*e.g.*, osteomyelitis, endocarditis, HIV), or pregnancy. Patients for whom a diagnosis was never elucidated were also excluded.

Data collection—Detailed demographic, clinical and laboratory data were collected by review of the medical records. Clinical data included the primary disease manifestations for lupus flares. Data regarding the severity of infection were collected. An infection was considered “severe” if it was associated with instability of vital signs, sepsis, mechanical ventilation, transfer to an intensive care unit for monitoring, or prolonged hospital stay. Laboratory data included ESR, CRP and white blood cell (WBC) count results from the University of Michigan Health System clinical laboratories. ESR was measured by the Westergren method, where blood is mixed with sodium citrate and allowed to stand in a 200mm long upright pipet filled to the zero mark. The rate of fall of red blood cells is measured at 1 hour. The normal ranges of ESR were 0–20 mm/hr for women and 0–15 mm/hr for men. An immunoturbidimetric method for measurement of serum proteins was used to quantify CRP. The normal range of CRP was 0.0–0.6 mg/dl.

Statistical analysis—Data distributions were examined and summary statistics were computed, expressed as means and standard deviations for continuous measures, or frequencies and proportions for categorical measures. Two-sample t-tests, χ^2 , and Fisher’s exact tests were used for comparisons of continuous and categorical measures, as appropriate. Pearson’s correlation was used to examine the correlation between variables. Univariate logistic regression was used to examine the associations between individual predictors and the outcome of flare versus infection; multivariable logistic regression was used to adjust for confounders. To avoid intra-subject correlation (for multiple hospitalizations within the same patient), models were re-run restricted to the first eligible hospitalization per patient. Analyses were performed using Stata 13.1 (StataCorp, College Station, TX).

RESULTS

Of the 557 patients screened from the Michigan Lupus Cohort, 39 SLE patients had eligible hospitalizations. 36 (92%) of the patients were female; racial distribution was 27 (69%) white and 12 (31%) black persons. At the first eligible hospitalization, mean age was 38.4 ± 12.5 years, and mean SLE disease duration was 9.6 ± 12.5 years. 30 of the 39 patients had a single hospitalization included this study.

A total of 53 hospitalizations (28 flares and 25 infections) were included in this study. Among these hospitalizations, fevers were objectively documented upon admission in 48 (90.6%). Predominant manifestations of the 28 SLE flares included: musculoskeletal in 11, neuropsychiatric in 8, chest pain (judged to be related to active SLE, *e.g.*, pleurisy, costochondriitis) in 5, cutaneous in 2, and other in 2. Among these 28 SLE flares, serosal features were present in 10 (4 pleuritis/pneumonitis, 6 not otherwise specified), and myositis in 3.

Infections were graded as mild/moderate in 16 and severe in 9. Infectious manifestations included bacteremia, meningitis, endocarditis, pneumonia, cellulitis, urinary tract infection, gastroenteritis, pelvic inflammatory disease, hepatitis, sinusitis and esophagitis.

ESR levels were similar for flares (mean $\pm$ SD: 50.7 ± 31.3 mm/hr) and infections (53.4 ± 34.5 mm/hr); $p=NS$. CRP levels were significantly higher for infections (11.2 ± 7.2 mg/dl) compared to flares (5.4 ± 6.5 mg/dl); $p=0.0035$ (Table 1). Likewise, CRP levels were significantly higher for infections graded as severe (15.4 ± 6.9 mg/dl) compared to mild/moderate (8.9 ± 6.5 mg/dl); $p=0.03$ (Figure 1). In addition, CRP trended higher for bacterial (13.3 ± 7.8 mg/dl) versus viral (7.2 ± 6.6 mg/dl) infections, though not reaching statistical significance. WBC count correlated positively with CRP ($r=0.4$, $p=0.004$), but not ESR ($r=-0.02$, $p=NS$). As presented in Table 1 and Figure 2, the proportion of flares versus infections varied according to ratio of ESR:CRP, with infections predominant for ratios of ≤ 2 , and flares predominant for ratios of > 15 ; $p<0.000$.

According to flare characteristics, CRP levels were higher for the 10 flares with a serosal component compared to the 18 flares without a serosal component [8.7 ± 8.3 vs 3.6 ± 4.6 ($p=0.04$), respectively]. Mean CRP levels corresponding to the 3 flares with a myositis component (7.4 ± 9.9) were similar to those characterized by serositis.

CRP levels were similar for the 19 patients currently on hydroxychloroquine compared to the 34 patients not taking hydroxychloroquine (7.2 ± 8.3 vs 8.7 ± 6.9 , $p=NS$). Likewise, we did not detect a difference in CRP levels according to statin use, though only 4 patients were taking statins (12.1 ± 9.8 statin vs 7.8 ± 7.2 no statin).

In univariate analyses evaluating the risk of flare compared to infection, ESR was not a significant predictor (OR 1.0, 95% CI 0.98, 1.01), but CRP was inversely associated with flare (OR 0.88, 95% CI 0.80, 0.97). The ESR:CRP ratio was positively associated with flare, where each unit increase in the ESR:CRP ratio was associated with a 13% increase in the odds of the etiology being attributed to SLE flare versus infection (OR 1.13, 95% CI 1.03, 1.25). WBC count was not a significant predictor when handled either as a continuous measure (OR 0.94, 95% CI 0.83, 1.06) or categorized as ≥ 10 versus <10 K/mm³ (OR 1.09, 95% CI 0.29, 4.13). Subset analyses restricted to the first hospitalization per patient did not substantively differ.

Results based on multivariable analyses are presented in Table 2. In the full model (Model A), adjusting for ESR, CRP, WBC count, disease duration, sex, race, and age, a positive association between ESR:CRP and flare was maintained (OR 1.16, 95% CI 1.00, 1.35; $p=0.056$). A second model (Model B) omitted ESR and CRP as individual covariates to avoid over-adjustment when modeled alongside their ratio; in this model the OR for ESR:CRP was slightly stronger (OR 1.17, 95% CI 1.04, 1.31; $p=0.009$). A third model (Model C) included ESR and CRP as individual covariates and omitted their ratio; in this model CRP was inversely associated with flare (OR 0.84, 95% CI 0.73, 0.96; $p<0.012$) but ESR was not significantly associated (OR 1.02, 95% CI 0.99, 1.05). Among these three models, Model B had the lowest values for the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC), indicating best fit. Together, these results indicate that

while CRP may be individually more informative than ESR in this setting, taking their relative values into account provides incremental information when differentiating between SLE flare versus infection. Similar to the univariate models, results from subset analyses restricted to the first hospitalization per patient remained similar for the multivariable models. Likewise, when the five hospitalizations with subjective fevers at presentation were omitted from modeling, there were no substantive differences in results.

DISCUSSION

We explored the relationship between two non-specific inflammatory markers – ESR and CRP – and their ability to distinguish between SLE disease flare and infection among patients with fever. To our knowledge, we report for the first time that quantifying the ratio of ESR to CRP provides added diagnostic value to individual ESR and CRP results. In general, previous studies have reported a disparity between ESR and CRP during SLE flares (1) characterized by robust ESR and blunted CRP responses (5,8,9,13,14). Several possibilities for this finding include the production of autoantibodies against CRP (15,16), and the effects of interferon- α (IFN- α), a molecule highly expressed in lupus disease activity (17,18), which may play a role in suppressing CRP levels by inhibiting CRP promoter activity and CRP secretion (19).

In this retrospective study of lupus patients presenting with fever, the ESR:CRP ratio was shown to be useful in differentiating between the infection and lupus flare. In the three cases with ratios <2 , the etiology of the fever was found to be infectious, and in 15 of 16 (94%) of cases with ratios >15 , the etiology of fever was ultimately attributed to lupus flare. These results suggest that a low ESR:CRP ratio may warrant aggressive search for infection and a lower threshold for initiation of antibiotic therapy in a febrile SLE patient. High ratios may encourage more expeditious treatment for lupus flare and a lesser concern for at least severe infection as a cause of fever in a febrile lupus patient.

Although our study found that CRP levels were significantly higher in cases of infection, particularly severe infections, an independent association did not persist in multivariable models including the ESR:CRP ratio. In assessing the levels of CRP across bacterial versus viral infection, our data confirmed previous findings of higher CRP levels in bacterial infections (20–22). Additionally, CRP levels were almost two times higher among those with pneumonia compared to those with any other type of SLE pulmonary manifestations.

ESR levels were not correlated with infection. This may reflect the standard method of measurement of the ESR in general, which provides only a crude guide to the extent of inflammation (13). While CRP is a plasma protein present in all humans released by hepatocytes in response to interleukin-6 during inflammation, the ESR is simply a measure of the rate of fall of erythrocytes when anticoagulated blood is placed in a vertical tube. The rate is directly correlated with the concentration of acute phase proteins, particularly fibrinogen, in the plasma that cause aggregation of erythrocytes (13). The rate of rise of fibrinogen in the acute phase response may be slower than that of CRP. Therefore, due to this indirect method of measurement, the ESR is influenced by multiple factors including concentration of plasma proteins as well as concentration, size and shape of erythrocytes.

Both measures also vary in the population in general: ESR rises with age and is higher in women compared to age-matched men (23), and CRP can vary with sex and race (3). We adjusted for these factors in multivariable modeling in the current study. Some data has suggested a reduction in CRP levels with the use of statins (24) and anti-malarials (25). We found no significant difference in CRP values across groups on or off hydroxychloroquine. The same was found for statin use, although numbers were low, with only four patients on statin therapy. The WBC count also was not predictive of flare versus infection in this study, when analyzed as either a continuous or categorical variable.

SLE manifestations of serositis have been associated with significantly higher CRP levels (26,27). The large inflammatory response and vasculitic component of serosal membrane involvement may be responsible for the elevated CRP in this group of patients (28). Thus, variation in CRP values across types of organ involvement in SLE has been proposed. Firooz *et al.* reported significantly higher hsCRP levels in patients with pulmonary disease compared to other types of organ involvement; the highest hsCRP levels in their study were in patients with pleuritis, pericarditis, pneumonitis, nephritis and myositis (10). Mochizuki *et al.* reported elevated CRP levels in SLE patients with pleuritis in comparison to those SLE patients with other pulmonary manifestations (such as interstitial pneumonia), suggesting that pleuritis is manifested by a large inflammatory cell process (28). Indeed, we found significantly higher CRP levels in flares with a serositis component compared to non-serositis flares.

Limitations of our study include its retrospective nature, and reliance on available health records that were not specifically designed to address our research question. Future prospective research is warranted to further investigate and validate the prognostic value of the ESR:CRP ratio and refine ratio cutoff points to optimize the ability to distinguish between flares and infection.

Our study demonstrates the potential utility of quantifying ESR:CRP ratios in the diagnostic setting. Indeed, multivariable models including ESR and CRP as a ratio rather than solely as separate variables were associated with the best model fit. This simple and objective measure may prove more clinically useful than either ESR or CRP alone, or WBC count, for more quickly elucidating a diagnosis and management plan in febrile SLE patients. Further research is necessary to replicate this finding in other lupus populations in a prospective manner.

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Figure 1. Comparison of CRP levels in SLE flares or infections graded as mild/moderate or severe

CRP levels were significantly higher for infections compared to flares ($p=0.0035$) and for infections graded as severe compared to mild/moderate ($p=0.03$).

Figure 2. Relative frequency of flares versus infections according to ESR:CRP ratio (categorized as ≤2, 2–15, or ≥15)

There was a significant difference in the distribution of flares versus infections according to ESR:CRP ratio ($p=0.000$).

Table 1
Non-specific markers of inflammation corresponding to episodes of flare versus infection

Results expressed as mean (SD) or frequency (%).

	Lupus Flare (n=28)	Infection (n=25)	P-value
ESR (mm/hr)	50.7 (31.3)	53.4 ± (34.5)	NS
CRP (mg/dl)	5.4 (6.5)	11.2 (7.2)	0.0035
ESR:CRP ratio			0.000
2	0 (0)	3 (12.0)	
2–15	13 (46.4)	21 (84.0)	
15	15 (53.6)	1 (4.0)	
WBC >10 K/mm ³	6 (21.4)	5 (20)	NS

Table 2

Odds ratios for flare versus infection, based on multivariable analyses

	Model A (Full) OR (95% CI)	Model B ^a OR (95% CI)	Model C ^b OR (95% CI)
ESR:CRP ratio	1.16 (1.00, 1.35)	1.17 (1.04, 1.31) **	NA
ESR (mm/hr)	1.00 (0.96, 1.04)	NA	1.02 (0.99, 1.05)
CRP (mg/dl)	0.99 (0.82, 1.18)	NA	0.84 (0.73, 0.96) *
WBC count (K/mm ³)	1.08 (0.90, 1.28)	1.07 (0.90, 1.26)	1.04 (0.87, 1.23)
Sex			
female	<i>referent</i>	<i>referent</i>	<i>referent</i>
male	2.79 (0.07, 105.93)	2.06 (0.09, 47.29)	3.16 (0.14, 70.87)
Race			
white	<i>referent</i>	<i>referent</i>	<i>referent</i>
black	1.11 (0.18, 6.74)	0.94 (0.22, 4.15)	1.15 (0.25, 5.27)
Age at visit (yrs)	1.02 (0.94, 1.11)	1.02 (0.94, 1.10)	1.02 (0.95, 1.09)
SLE duration (yrs)	0.90 (0.80, 1.01)	0.90 (0.80, 1.01)	0.91 (0.82, 1.01)

* p < 0.05.

** p < 0.01

^a ESR and CRP not included as individual covariates

^b Ratio (ESR:CRP) not included

Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) for models, respectively, as follows: Model A (65.4, 82.6); Model B (61.5, 74.9); Model C (70.8, 86.1)