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Is initial C-reactive protein level associated with corticosteroid use in lupus erythematosus patients during a bacterial infection episode?

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ABSTRACT

Objective: C-reactive protein (CRP), a marker for inflammation, indicates bacterial infection in systemic lupus erythematosus (SLE) when markedly elevated. Our study investigated the association of regular corticosteroid or immunosuppressant use with initial CRP level in febrile SLE patients with bacterial infection.

Methods: This retrospective cohort study included adult SLE patients (18 years of age or older) who presented with fever at the emergency department from January 2008 to December 2012. Data were retrieved from our institutional database.

Results: CRP levels in the total 193 patient database were significantly increased in the bacterial infection group compared to the no infection and non-bacterial infection groups. Seventy-eight (86.7%) of the 90 patients in the bacterial infection group took regular corticosteroids (mean equivalent dose of prednisolone 0.33 ± 0.26 mg/kg/day) and 55 (61.1%) used immunosuppressants. Mean CRP level in the bacterial infection group was 97.8 mg/L. CRP level was lower in patients using corticosteroids, but the difference between users and nonusers of corticosteroids was not statistically significant ($p = 0.367$). The difference in CRP level between immunosuppressant and non-immunosuppressant users was also not significant ($p = 0.599$). The Spearman test found no correlation between corticosteroid dosage and CRP level ($p = 0.911$).

Conclusion: Initial CRP level was not significantly associated with regular corticosteroid or immunosuppressant use in SLEs patients during a bacterial infection episode, and CRP level was not dose-dependently related to daily corticosteroid use. An elevated CRP level might be an appropriate marker for bacterial infection at the emergency department for febrile SLE patients.

1. Introduction

Fever is a common presentation at emergency departments (EDs) in patients with systemic lupus erythematosus (SLE) [1,2]. The differential diagnosis of fever in lupus patients is broad and includes lupus flare, and bacterial, viral, or fungal infection. Lupus flare results in tissue damage and inflammation, i.e., symptoms and signs that are similar to those of infections [3,4]. The fever pattern is not helpful for diagnosis, especially because the course of this disease is unpredictable and its stage uncertain. In addition, most patients are taking immunosuppressants or corticosteroids regularly, drugs that can mask the clinical findings and delay the diagnosis. But it t is important for emergency physicians to be able to identify bacterial infection in order to start antibiotic treatment promptly [5–7].

Certain laboratory parameters can distinguish infection from disease flare in SLE [8]. C-reactive protein (CRP) is a marker of inflammatory and infectious processes [9]. But in contrast to the elevations of CRP level seen in other inflammatory diseases, such as rheumatoid arthritis and ankylosing spondylitis, the elevation of CRP during lupus flare is modest [10,11], and therefore marked elevation of CRP level in a febrile lupus patient indicates a bacterial infection [12–14].

However, several studies have demonstrated the association of corticosteroid and immunosuppressant use with lower CRP levels [15–18], and this association might interfere with the use of CRP as a

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diagnostic tool in SLE. Whether there is an association of CRP level with the regular use of corticosteroids and immunosuppressants and whether a dose-response relationship exists between corticosteroid use and CRP level in lupus patients with bacterial infection are major concerns. Therefore, this study investigated CRP levels at initial presentation in the emergency department (ED) of febrile SLE patients with no infection, non-bacterial infections, and bacterial infections, and the association between regular corticosteroid or immunosuppressant use and initial CRP level in the ED in the group with bacterial infection.

2. Materials and methods

2.1. Study design and patient selection

This retrospective cohort study was conducted at a university-affiliated teaching hospital averaging approximately 130,000 visits annually. The Hospital Ethics Committee on Human Research reviewed and approved the study protocol and exempted the study from the need for informed consent.

The study cohort was adult lupus patients (18 years of age or older) admitted to our hospital through the ED because of fever, during the period from January 2008 to December 2012. Fever was defined as a tympanic temperature >37.8 °C at ED triage. Patients with uncertain diagnosis, no CRP results or incomplete records were excluded. Patients were then divided into three groups: those with bacterial infections, those with non-bacterial infections (mostly viral infections), and those with no infection. Those with bacterial infections, had the infection diagnosed before their discharge. The diagnosis of bacterial infection was made on the basis of clinical findings of a confirmed infection focus, positive cultures, and positive responses to antibiotic treatment during hospitalization. For analysis, patients with bacterial infections were further divided into those with and without the chronic use of corticosteroids, and those with and those without the chronic use of immunosuppressants.

2.2. Hospital and outpatient care

Lupus patients were followed up regularly by board-certified rheumatology specialists at our outpatient department, and were prescribed corticosteroids or immunosuppressants by rheumatology specialists based on their clinical judgment and discretion. In our ED, the emergency physician functions as a primary care provider, takes the medical history, and performs the physical examination after triage. There were no guidelines on selection of routine laboratory tests, including CRP, for monitoring such a condition during the study period. Tests were ordered based on the clinical judgment and discretion of the emergency physician. The patients were then treated and admitted (or sent home) after discussing their test results with the physician. Those who were admitted were cared for by rheumatology specialists or residents under their supervision. The final diagnosis was made according to the clinical course, response to treatment, and test results.

2.3. Data collection

Adult patients who were admitted to the ED with a diagnosis of SLE (International Classification of Diseases Code, 9th revision, [ICD-9 code 710.0]) and fever at triage were enrolled. Data were retrieved via computer from the admission registry of the ED. The first author reviewed previous medical records to confirm the diagnosis of SLE according to the revised American College of Rheumatology criteria for the classification of SLE [18]. A trained study assistant who was blinded to the study purpose performed the chart review and extracted the data using a standardized template, clear definitions, and specific codes. The first author provided quality improvement feedback after the data analysis. Demographic data and results of laboratory tests were collected. The medication history was reviewed, including corticosteroids and immunosuppressive agents prescribed in the out-patient-department (OPD). In addition, the prednisolone equivalent dose of other corticosteroids prescribed within one month before the ED visit was calculated using a relative potency ratio [19]. Infection sites were recorded, such as respiratory tract, skin and mucosa, central nervous system, gastrointestinal tract, musculoskeletal system, peritoneum and urinary tract [20,21]. Admission into the intensive care unit (ICU) and mortality during hospitalization were also recorded.

2.4. Statistical analysis

Mean ± standard deviation (SD) and median (interquartile range) were presented for continuous variables with normal distributions and those with skewed distributions, respectively. Frequency as well as percentage for categorical variables was computed as well. Analysis of variance (ANOVA) was performed to test differences in continuous variables between groups, and was replaced with the Kruskal-Wallis test when data distributions were skewed. Bonferroni's correction method and Mann-Whitney *U* test were then performed for post-hoc tests when a significant result was revealed by ANOVA or by the Kruskal-Wallis test. The Mann-Whitney *U* test was also carried out to compare CRP level between patients taking immunosuppressants and those not and those taking corticosteroids and those not. Log10 transformation was applied before performing a generalized linear model for comparisons of CRP levels between groups after controlling for the impacts of baseline differences. The CRP level was illustrated by bar charts, presented as of mean ± standard error. Spearman's rank correlation was carried out to examine the correlation between the CRP level and dose of prednisolone equivalent. All statistics were two-sided and implemented on PASW statistical software (version 22.0, IBM Corp., Armonk, NY). A $p < 0.05$ was considered statistical significance. When post-hoc tests were necessary, the p value was adjusted to 0.017 (0.05/3) or 0.008 (0.05/6).

3. Results

Of the 383 patients enrolled in this study, data from 190 patients were excluded because of no data on corticosteroid use, incomplete records, or no data on the CRP level; 193 patients were then included for analysis. (Fig. 1)

Patients' characteristics are shown in Table 1. The three groups of patients (no infection, non-bacterial infection, bacterial infection) were similar in gender, blood pressure, corticosteroid use and immunosuppressant use. However, patients with bacterial infection were significantly older and had significantly higher CRP levels than those without infection or with non-bacterial infections. Significantly higher body temperature (38.9 °C vs. 38.6 °C) and higher WBC counts ($9.1 \times 10^3/\mu L$ vs. $6.4 \times 10^3/\mu L$) were found in the bacterial infection group compared to those with no infection. And the bacterial infection group had a significantly higher heart rate (119.8 beats/min vs. 109.8 beats/min) and respiratory rate (20.7 breaths/min vs. 19.4 breaths/min) than the non-bacterial infection group. There was a trend for a greater percentage of those with bacterial infections to have a longer stay in the ICU (15.6% vs 3.4%) and to die (12.2% vs. 1.8%) than those with non-bacterial infections, and this trend was statistically significant ($p = 0.018$) for death.

CRP levels according to steroid/no steroid use and immunosuppressive/no immunosuppressive agent use are shown in Fig. 2. Seventy-eight (86.7%) of the patients with bacterial infection were