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Immune cytokine imbalance and hematological disturbances in systemic lupus erythematosus patients

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Abstract

Lupus nephritis is a severe condition that develops due to the immune complex deposition on renal tissues, which plays a key factor in the development of the disease as well as long-term complications. Thus, it is important to diagnose the disease on time and implement specific treatment strategies in order to reduce the damage to the kidneys and improve the prognosis of patients. Its pathophysiology entails the interplay, the interaction of immune system dysregulation and genetic predisposition and some cytokines are involved. In the current study we accessed 40 systemic lupus erythematosus (SLE) patients, clinically diagnosed in the Rheumatology Unit at Baghdad Teaching Hospital, and 40 individuals who were used as normal controls. Serum concentration of interleukin-39 (IL-39) was quantitatively analyzed and extensive hematological assessments made. Genetic research was also done through the Sanger sequencing to find possible immunogenetic causes of the disease. Blood levels of IL-39 were significantly higher in SLE patients than control (p<0.0011). Interestingly, IL-39 levels had a high correlation with disease activity ratings, and it indicates that the biomarker can be a good indicator to follow the progression and the severity of the disease. Based on the hematological parameters, the levels of hemoglobin of the patients were below those of the control group (p<0.01), the erythrocyte sedimentation rate was much higher (p<0.001). These findings indicated that IL-39 is highly up-regulated in SLE patients, which highlights the most urgent role of this cytokine in the immunopathology of the disease. In conclusion our data reaffirms the idea that IL-39 can be a new biomarker of gauging disease activity and can be helpful in shaping more specific clinical platforms of treatment.

Keywords: Interleukin 39, Hemoglobin, ESR, White Blood Cells, SLE.

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Introduction

Systemic lupus erythematosus is a complicated disease, which entails multiple immunopathological mechanisms, which results in varying clinical manifestations that could involve multiple organ systems.[1, 2] This diversity is a grave impediment to accurate diagnosis, categorisation and effective treatment planning.[3, 4] To make analysis, at present, it is combined with biochemical and serological tests and clinical examinations.[4, 5] Because the early identification of the disease is linked to desirable patient outcomes, reliable biomarkers

that could consistently reflect the disease activity and distinguish SLE among other autoimmune disorders ought to be identified. Such biomarkers will preferably be an expression of the underlying immunological activation and systemic inflammatory processes.[2, 5] It is desperately needed in new diagnostic procedures and better knowledge of pathophysiology.[2, 4, 6] The most promising potential of the non-invasive biomarkers is to be diagnosed much earlier and thus create an opportunity to pursue even more specific approaches to treatment.[1, 2] Immunological indicators have traditionally been regarded as good candidates not only to early diagnosis, but also to learn the detailed pathogenesis of SLE.[4] Inflammatory and immune responses, mediated by cytokines, obviously place them at a central role in disease activity. The principle of their application in diagnosis and continuous illness monitoring is grounded on their involvement in the pathophysiology of SLE.[4–6]. Particularly within this setting, interleukins attracted more attention as major regulators that take part in immune suppression, disease development, and detection not only in SLE but also in several other autoimmune diseases.[7–9] Members of the interleukin-12 (IL-12) family interleukins have clinical relevance in disorders through pro-inflammatory signalling pathways and therefore attracted attention.[4, 10] Interleukin-39 (IL-39) is a newly discovered αβ heterodimeric glycoprotein family-wise belonging to this family.[11, 12, 13, 14] Available data indicate it contributes to inflammatory cascades, hence could be involved in numerous clinical disorders.[15] Diseases like ankylosing spondylitis, therefore leading to the value of IL-39, which might distinguish the patients from normal controls.[15] Chronic diseases with high levels of IL-39 are immunologically unregulated and also have dysfunction in their heart; however, exact mechanisms are still unexplored, but pathways identified implied association with various chronic inflammatory and autoimmune diseases.[13, 15, 16] Members of the IL-12 family interleukins have clinical relevance in disorders through pro-inflammatory signalling pathways and therefore attracted attention.[4, 10] Interleukin-39 (IL-39) is a newly discovered αβ heterodimeric glycoprotein family-wise belonging to this family.[11, 12, 13, 14] Available data indicate it contributes to inflammatory cascades, hence could be involved in numerous clinical disorders.[15] Diseases like ankylosing spondylitis, therefore leading to the value of IL-39, which might distinguish the patients from normal controls.[15] Members of the IL-12 family interleukins have clinical relevance in disorders through pro-inflammatory signalling pathways and therefore attracted attention.[4, 10] Interleukin-39 (IL-39) is a newly discovered αβ heterodimeric glycoprotein family-wise belonging to this family.[11, 12, 13, 14] Available data indicate it contributes to inflammatory cascades, hence could be involved in numerous clinical disorders.[15] Diseases like ankylosing spondylitis, therefore leading to the value of IL-39, which might distinguish the patients from normal controls.[15] While some investigators consider IL-39 primarily as a mouse-restricted cytokine, other researchers have demonstrated the presence of detectable IL-39 in human specimens, supporting required additional studies in humans.[13]

Subjects and Methods

The study was conducted between January and April 2023 and included 80 female volunteers: 40 patients with systemic lupus erythematosus (SLE) and 40 healthy control subjects who attended the Rheumatology Unit of Baghdad Teaching Hospital.

Blood Collection

Using a single-use syringe and sterile venipuncture, 5 ml of blood was collected from each patient. An aliquot of 2 ml of the blood samples were collected in gel tubes and then stored at -20 °C. and 1.5 ml of the blood sample was kept in a sodium citrate tube for detection of the erythrocyte sedimentation rate (ESR), 1.5 ml of the blood sample (whole blood) for the hematological test.

Sampling Criteria

Patients and controls group were recruited from the Rheumatology clinics and wards based on inclusion criteria: age ≥18 years, diagnosis of SLE per 2019 EULAR/ACR criteria and no active

infections or other autoimmune diseases. Exclusion criteria included pregnancy, recent blood transfusions, use of non-standard biologic therapies, and chronic liver or kidney diseases unrelated to SLE. Disease activity was evaluated using the SLEDAI-2K score, which considers clinical and laboratory features over the past 10 days, including arthritis, rash, renal involvement, hematological abnormalities, and relevant antibodies.

Immune Assay

Anti-IL-39 antibodies in human serum were quantified by a commercially available enzyme-linked immunosorbent assay (ELISA) kits (Catalogue No. SL12345HU, SunLong Biotech Co., China). The assay had a sensitivity of 5 pg/ml and a detection range between 10 and 2000 pg/ml. Serum samples and standards were added to microplates pre-coated with IL-39 antigen and incubated as specified in the kits. After washing, a substrate solution was applied to develop the final color, and absorbance was measured at 450 nm.

Hematological Investigations

We performed hematological tests which are related to SLE disease as follows: Total white blood cell (WBCs) count, hemoglobin (Hb) level, erythrocyte sedimentation rate (ESR). The Westergren assay technique was used to determine the ESR. The average values for women were 0-20 mm/hr.

Statistical Analysis

Data analyses were done in SPSS V26 and in the form of mean and SD. Student's t-test was used to test group differences, and Pearson correlation was used to determine that IL-39 and disease activity markers were correlated. The level of statistical significance was determined as $p<0.05$.

Results

Hematological Manifestations

We used blood cell hematology analyzer counts and identifies accurately at rapid speed.[13] The CBC is the most regularly ordered test by doctors to determine the health conditions of the patients. A comparative analysis of hematological indices revealed a statistically significant variance between SLE patients and control subjects. This was characterized by a significant reduction in the count of the white blood cells in the SLE group (4.1 ± 1.6 10 9 /l) than controls (8.1 ± 1.8 10 9 /l, $p < 0.001$) which indicated existence of leukopenia that is common in autoimmune disease pathology. Concentration of hemoglobin was also lower among patients (11.2g/dl) compared with control individuals (14.1 g/d, $p < 0.01$) as evidence of anemia that could be a symptom of chronic inflammation or a renal functional malfunction of lupus. Moreover, there was a striking increase in ESR in the SLE group (46.0 mm/hr) compared to the control one (15.0 mm/hr; $p <0.001$), with the ongoing process of systemic inflammation, as showed in Figure 1.

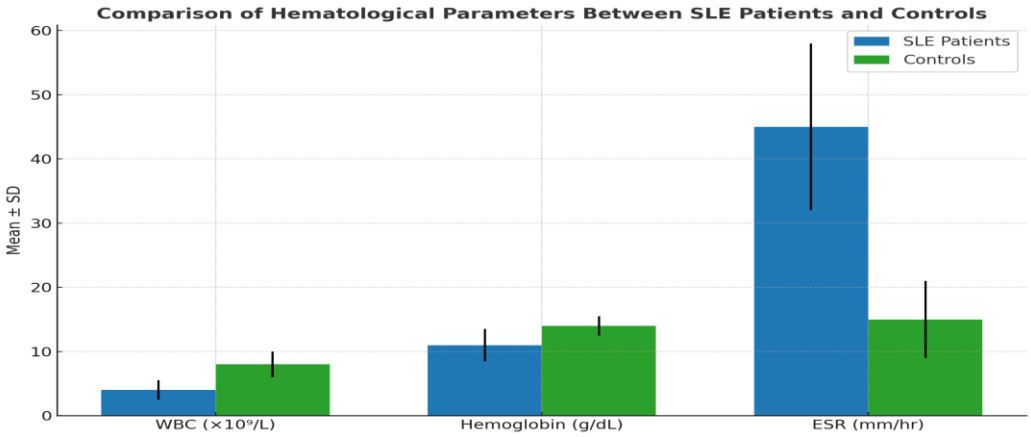

Figure 1. Comparison of hematological parameters in systemic lupus erythematosus (SLE) patients and controls.

The results demonstrated a significant increase in serum IL-39 levels among SLE patients when compared to the normal control group. Patients with SLE exhibited a mean IL-39 concentration of 12.78 ± 2.59 ng/l, notably significantly higher than the 9.98 ± 0.76 ng/l recorded in the control subjects (p = 0.0011)**.** This could imply that the high levels of IL-39 could be correlated with the underlying biological mechanisms that lead to SLE, as depicted in Figure 2.

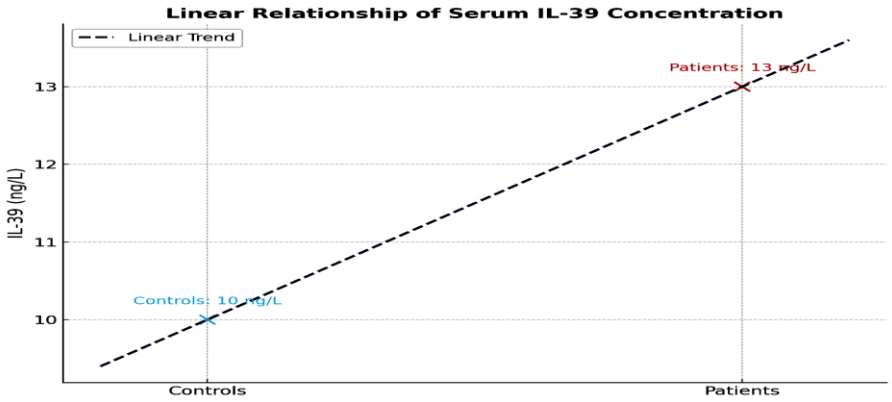

Figure 2. The mean IL-39 levels of the systemic lupus erythematosus (SLE) patients and controls.

Both post hoc tests of one-way analysis of variance (ANOVA) and LSD tests have proven that the differences in serum IL-39 levels were statistically significant among the various study groups (p= 0.003). Nonetheless, differences between patients with inactive SLE and the controls were not statistically significant, which could be due to a possible threshold effect or overlap between remission and baseline levels of IL-39.The highest mean was observed in the patients with active and severe SLE with an IL-39 level of 16.66 ± 3.10 ng/l. This concentration decreased gradually with the lessening severity of the disease with active moderate cases having a mean of 12.55 ± 1.39 ng/l and inactive SLE cases at 10.93 ± 1.58 ng/l. On the other hand, the control group recorded the lowest IL-39 concentration at 9.00 ±1.08 ng/l .These data indicate that there is a close relationship between high serum levels of IL-39 and high levels of disease activity in SLE patients. The fact that levels of IL-39 fell progressively with milder disease manifestations can be viewed as evidence of its possible use as a potential biomarker of disease severity and monitoring activity as shown in Figure 3.

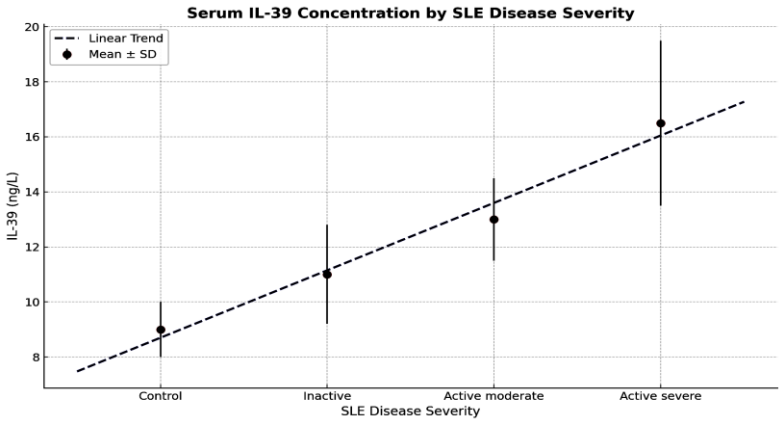

Figure 3. Mean concentration of IL-39 in systemic lupus erythematous (SLE) and control.

Correlation between hematological variables and IL-39 concentration

The hematological anomalies seen in SLE patients, i.e., leukopenia, anemia, and high ESR were noted to be directly related to upsurge in serum IL-39 levels. The direct contribution of the IL-39 to the persistence of systemic inflammation to boost it seems apparent in the fact that the distribution of the IL-39 levels and ESR was positively correlated. Conversely negative correlations between IL-39 and white blood cell count (WBC) count and hemoglobin concentration suggest the possibility that IL-39 can cause hematologic suppression, either by bone marrow dysregulation or peripheral immune-mediated lysis. The evidence provided in these studies concentrates on IL-39 as a possible immunoinflammatory mediator between cytokine over-proliferation and typical hematologic abnormalities in SLE (see Figure 4).

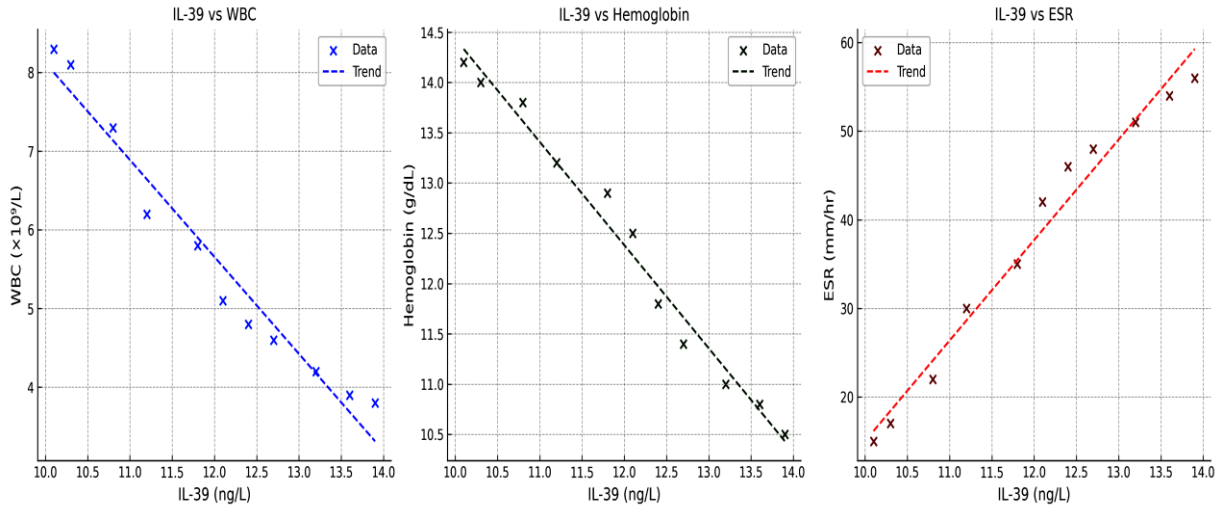

Figure 4. Relationship between IL-39 concentration and white blood cell count (WBC), hemoglobin, and erythrocyte sedimentation (ESR).

Discussion

One of the most widespread clinical problems that can be detected in SLE is hematological abnormalities that are commonly associated with immune dysregulation and chronic systemic inflammation. The hematologic abnormality that was found to be most common in this study was anemia found in 56% of the SLE patients followed by leukopenia occurring in 50% percent of the SLE patients. These prevalence levels are consistent with the past regional and international surveillance data, although they vary due to variations in genetic backgrounds, nutritional status, and environmental exposures, as well as access to health care. As an example, the prevalence of anemia in people with SLE was 64.96%, 60%, 75% and 58% in Pakistan, the USA, Saudi Arabia, and the UAE, respectively.[16,17,18,19] On the same note, it has been reported that leukopenia occurs across a wide range in various populations with a range of 23.5% - 57.3% in the Oman, China, and Thailand populations.[20,24] Leukopenia in SLE is multifactorially pathophysiological. It also involves immune-mediated bone marrow suppression, immune complex-mediated cytopenia, frequent infections, and drug-induced bone marrow toxicity.[25, 26] All these processes help to cause a decrease in the number of WBC in the periphery, which affects the host defense and predisposes the patient to infections. SLE anemia has also been related to skewed inflammatory mechanisms due to high production of hepcidin, a factor that governs iron metabolism and reduces the available iron to be used in the production of red cells, leading to anemia of chronic disease.[25] This inflammatory anemia has low hemoglobin level, a phenomenon that we always see in our cohort. Further, the ESR was also significantly higher in SLE patients than in controls, which are consistent with its non-specific but strong correlation with systemic inflammation, and disease activity.[29-33] High ESR is prompted by accelerated circulating immunoglobulins and acute-phase proteins, which denote continuous immune complex deposition and the engulfment of inflammatory cascades in different tissues.[29, 30]

At the same time with the observed hematologic alterations, our study showed that the concentration of IL-39 in patients was significantly higher, with the most significant values in patients showing severe manifestations of the disease, followed by moderate manifestations.[48-50] Even though the exact role of the IL-39 in human disease processes has not been elucidated, experimental models of lupus have shown increased levels of IL-39 during active disease periods and activation of pro-inflammatory factors signal transducer and activator of transcription 1 (STAT1) and STAT3 that enhance activation of immune cells and cytokine secretion.[48-50] A positive correlation between IL-12 family cytokines, indicating the implication in the immunopathogenesis and progression of SLE, was also reported. Furthermore, higher levels of IL-39 were reported in additional autoimmune conditions including rheumatoid arthritis, suggesting the involvement of IL-39 in widespread inflammatory reactions.[34, 35] Notably, we showed strong correlations between IL-39 concentrations and important hematological variables, suggesting the overlap between systemic inflammation and hematologic instabilities in SLE. Namely, IL-39 concentrations were positively related to WBC numbers, implying that IL-39 can cause or represent the activation and growth of leukocytes to stop the inflammatory flares. In turn, IL-39 was negatively correlated with hemoglobin levels and this is in line with cytokine-mediated erythropoiesis inhibition and anemia of chronic disease development. Besides, there was also a massive positive relationship between IL-39 and ESR that backs up its potential role as a predictor of systemic inflammation and the resultant disease activity. These correlations are consistent with the earlier research findings on the influence of cytokine networks on the hematologic defects of autoimmune diseases.[36, 41] SLE exhibits a complex immunopathology with a tight regulatory control of pro-inflammatory cytokines that encourage immune regulation and phases of suppression.[39, 41] The current

work will enhance the research in the given area and will consider less studied interleukins, including IL-35, IL-37, and IL-39, showing their changed levels in SLE patients and evidence of their recommendations as biomarkers and therapeutic targets. To eliminate the confounding factors that are associated with sex, only female patients were enrolled in this study as SLE has been shown to have a strong female predominance with a female: male ratio of about 9:1.[42, 43] Of note, men tend to have worse patterns of clinical phenotype, higher frequencies of the involvement of kidneys, which may be related to disparities in hormonal physiology, such as estrogen effects on the modulation of immune responses.[44-45] Summing up, it is possible to conclude that hematological abnormalities were one of the key characteristics of SLE and a new cytokine, IL-39, associated with the disease activity and hematologic indicators, may be assessed. The results indicated that IL-39 is a possible useful biomarker to control the disease progression and it can also be used as a parameter dictating directed immunotherapeutic solutions.

Author Contributions

SSF, collected the data and wrote the draft of the manuscript. RTM, proposed the topic of this research. MKQ, designed the study, and revised draft of the manuscript.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical approval

The study protocol was reviewed and approved by the Ethics Committee of the Biotechnology Department, College of Science, University of Baghdad.

Informed consent

Written informed consent was obtained from all participants before inclusion in the study.

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