Original Research Article

Study of serum level of Interleukin 33 in Systemic Lupus Erythematosus patients

Abstract:

Background: Systemic lupus erythematosus (SLE), is a chronic disease in which the immune system of the body attacks body tissues in multiple body systems, so it is called autoimmune disease. Arthritis, skin rash, photosensitivity and nephritis are the most common clinical presentation in SLE. Interleukin 33 (IL-33), is a one of the interleukins family and it is established that IL-33 is central in inborn and acquired immunity. Historically, IL-33 receptor was discovered first on surface of T helper 2 cells and not T helper T1 cells.

Aim: Measuring Interleukin-33 level in serum of SLE patients and its relation to clinical presentation, activity and severity of the disease.

Subjects and Methods: This study had been conducted at Clinical Pathology and Internal Medicine Departments-Tanta University Hospital from March 2019 to December 2019 on 80 subjects

Results: The affected females were at childbearing period and the incidence among gender is higher for females than that for males which reflects the hormonal role in SLE development. Serum creatinine, blood urea nitrogen, ESR levels were increased significantly in SLE patients than control group. There was a significant increase in serum IL-33 levels in SLE patients than control group indicating that IL-33 has a role in pathogenesis of SLE. There was significant difference of Hb, platelet count, ANA, and anti ds-DNA between SLE patients and control group. There was a positive significant correlation between IL-33 and serum creatinine, ESR, CRP and SLEDAI. The most common feature was arthritis (88.3%) of patients, followed by skin rash (60.0%) of patients.

Conclusion: IL-33 level in patients with SLE were significantly higher than that in control group and its level was significantly related to disease activity. This indicated that, IL-33 has a role in pathogenesis of SLE. So, IL-33 can be used as a diagnostic and a prognostic marker.

Keywords: Interleukin 33, Systemic Lupus Erythematosus patients

Introduction:

Systemic Lupus Erythematosus is one of autoimmune diseases. It is characterized by chronic immune activation of unknown etiology. It is multisystem affection disease involving skin, joints, kidney, blood vessels and nerves [(1)].

Multiple factors are linked with development of Systemic Lupus Erythematosus as: genetics, ethnic, immunoregulatary, hormonal and environmental factors [(2)].

Immune system disorders of the immune system are involved in the development of Systemic Lupus Erythematosus [(3, 4)].

Cytokines play a promoting role in the maturation, activation and differentiation of a variety of immune cells involved in the immune regulation of systemic lupus erythematosus [(5)].

Interleukin-33 is a cytokine and a member of the Interleukin-1 family. It is expressed by immune cells such as macrophages, dendritic cells, in epithelium and endothelium [(6)].

Various studies found a correlation between Interleukin-33 and autoimmune diseases including severity of the disease [(7, 8)].

Subjects and Methods:

Subjects:

This study had been conducted at Clinical Pathology and Internal Medicine Departments-Tanta University Hospital from March 2019 to December 2019 on 80 subjects divided into two groups:

Group (1): 60 patients having Systemic Lupus Erythematosus disease according to American College of Rheumatology (ACR) classification criteria for [9].

Group (2): 20 apparently healthy persons as a controlled group.

Ethics committee permitted our work after informed consents from all study subjects.

Inclusion criteria:

1. Apparently healthy persons and patients with Systemic Lupus Erythematosus were included in the study.
2. All subjects ranging from 18-75 years.

Exclusion criteria:

1. Patients with other systemic diseases.
2. Patients with other auto immune diseases.
3. Malignancy.
4. Confusion or coma patients.
5. Those who can not cooperate.
6. Bronchial asthma or atopic dermatitis.
7. Refusal to consent.

All patients in this study had been subjected to the Following:

A- Complete history taking:

1-Personal history:

Name, age, sex, residency, and number of family members**.**

2-History of present illness:

- Age at first presentation of the disease.
- Disease duration.
- Presence of renal, mucocutaneous, musculoskeletal, neuropsychiatric, respiratory, cardiovascular and gastrointestinal manifestations.
- Presence of complications.

3-Past history:

Hospital admission, disease, drug intake and operation.

4-Family history:

Similar condition in the family and consanguinity.

B- Complete clinical examination

C- Laboratory investigations:

A) Routine Laboratory Investigations:

1) Complete Blood Picture (CBC).

2) Erythrocyte Sedimentation Rate (ESR).

3) C-reactive protein (CRP).

4) Kidney function tests (creatinine and BUN).

5) Urine analysis.

6) ANA and anti-dsDNA antibody.

B) Specific Laboratory Investigations:

Interleukin-33 level was estimated by sandwich Enzyme-Linked Immuno Sorbent Assay (ELISA).

Statistical Analysis

Collected data were recorded then presented and analyzed statistically by computer using SPSS version 22(SPSS Inc. Chicago, IL, U.S.A) as the following: Chi-square test and Fisher's exact test, wherever appropriate, were used for data analysis. Mann-Whitney-U tests were applied to compare the continuous variables between the two groups. Other parameters were assessed with Spearman's correlation test. P value equal to or less than 0.05 was considered significant. P value more than 0.05 was considered not significant.

Results:

Regarding to subject's interlukin-33, **(Table 1);** show that IL-33 in patients group ranged between 61.2-729.4 ng/l with mean±S.D. 185.3±181.3, while in control group it ranged between 12.0-35.7 ng/l with mean±S.D. 21.1±7.1. There were statistically significant differences between groups where P<0.001.

Table (1): Comparison between two groups as regard to subject's interlukin-33.

IL-33 (ng/l)	Patients Group (n=60)	Control Group (n=20)	P Value
Range	61.2-729.4	12.0-35.7	<0.001*
Mean± S.D	185.3±181.3	21.1±7.1	
Median	93.6	19.3	

Regarding to patient's grade, **(Table 2);** show that 19(31.7%) were mild, 5(8.3%) were moderate, 20(33.3%) were high and 16(26.7%) were very high**.**

Table (2): Patient's grade.

Grade	Patients Group (n=60)	
	No.	%
Mild	19	31.7
Moderate	5	8.3
High	20	33.3
Very High	16	26.7
Total	60	100

Regarding to disease activity, **(Table 3);** show that 53 (88.3%) had arthritis, 36(60.0%) had rash, 35(58.3%) had photosensitivity, 20 (33.3%) had nephritis, 20(33.3%) had hematuria, 16 (26.7%) had proteinuria, 10(16.7%) had alopecia, 9(15.0%) had pyuria, 7(11.7%) had oral ulcer, 6(10.0%) had vasculitis, 6(10.0%) had visual disorder, 6(10.0%) had thrombocytopenia, 5(8.3%) had myositis, 5(8.3%) had leukopenia, 4(6.7%) had fever, 3(5.0%) had CVD, 3(5.0%) had lupus headache, 2(3.3%) had pleurisy and 1(1.7%) had psychosis.

Table (3): Patient's SLE disease activity.

SLE disease activity	patients group (n=60)	
	No.	%
Arthritis	53	88.3
Rash	36	60.0
Photosensitivity	35	58.3
Nephritis	20	33.3

Hematuria	20	33.3
Proteinuria	16	26.7
Alopecia	10	16.7
Pyuria	9	15.0
Oral Ulcer	7	11.7
Vasculitis	6	10.0
Visual Disorder	6	10.0
Thrombocytopenia	6	10.0
Myositis	5	8.3
Leukopenia	5	8.3
Fever	4	6.7
CVD	3	5.0
Lupus Headache	3	5.0
Pleurisy	2	3.3
Psychosis	1	1.7

Regarding to correlation between IL-33 and laboratory parameters, (**Table 4)** show that there was highly significant positive correlation between IL-33 and CRP, ESR, creatinine and SLEDAI and there was no significant positive or negative correlation between IL-33 and Hb, TLC, platelet count and BUN.

Table (4): Correlation between IL-33 and laboratory parameters

	IL-33	
	r	**P**
CRP	0.727	<0.001*
ESR	0.963	<0.001*
Hb	- 0. 231	0.073
TLC	- 0.207	0.109
Platelets	- 0.116	0.324
BUN	0.219	0.098
Creatinine	0.966	<0.001*
SLEDAI	0.854	<0.001*

Discussion:

In our study, level of interleukin-33 in the patients group ranged between 61.2-729.4 ng/l with mean±S.D. 185.3±181.3, while in the control group it ranged between 12.0-35.7 ng/l with mean±S.D 21.1±7.1. There was statistically significant difference between groups.

Guo et al., (2016) [10], ***Toama et al., (2017)*** [8] Found that there was significant increase in IL-33 levels in lupus patient compared to control group

A different results concluded by ***Mok et al., (2010)*** [11] who reported no difference in IL-33 levels between lupus and healthy individuals and levels were below detection in both groups but this can be due to different methods of assessment.

In our study, according to disease activity, patients categorized as 19(31.7%) mild, 5(8.3%) moderate, 20(33.3%) high and 16(26.7%) very high. The disease activity index (SLEDAI) ranged between 2 – 58 with a mean value of 16.4±15.0.

In ***Toama et al., (2017)*** [8]**,** Patients were categorized into mild, moderate, high and very high disease activity and we can notice that most of the chosen sample had very high disease activity (45.8%). SLEDAI of the lupus cases had a range between 4 and 40 with a mean value 18.2 with standard deviation ± 8.5.

According to our results, the most frequent clinical findings observed in SLE patients were arthritis (88.3%) and malar rash (60%) followed by photosensitivity (58.3%), nephritis

(33.3%), hematuria (33.3%) and proteinuria (26.7%). After examination of hair, 10 patients (16.7%) had alopecia. Other less frequent clinical findings included pyuria (15%), oral ulcer (11.7%), vasculitis, (10%), visual disorder (10%) and thrombocytopenia (10%).

A study by ***Wislowska et al., (2008)***[12] showed different SLE symptoms frequencies especially photosensitivity which was up to (90%) in his study group and haematological monifestations were observed in half of his study group (50%).

Positive significant correlation was found in our study between IL-33 and ESR, CRP, serum creatinine and SLE disease activity index (P<0.001). No significant correlation was detected between the level of IL-33 and blood urea nitrogen.

In this study, there was no significant correlation between the level of IL-33 and TLC, platelet count and Hb level wich was similar to the results by ***Toama et al., (2017)*** [8]

In disagreement with our results, ***Yang et al., (2011)*** [13] reported negative significant correlation between IL-33 and platelet count.

Guo et al., (2016) [10] concluded that CRP and ESR were positively correlated with serum IL-33 levels which implies that IL-33 might have a role as an acute phase reactant. This also was consistent with previous results of ***Toama et al., (2017)*** [8], ***Yang et al., (2011)***[13] and ***Li et al.,(2014)*** [14]***.***

Recommendations:

- It is desirable to validate the results of the present study on a higher number of patients due to the small sample size, possibly through a multicenter study.
- Measuring serum level of IL-33 before and after treatment of SLE patients may clarify more about the role of this interleukin and its precise involvement in the pathogenesis.
- Using (anti IL-33 antibodies) as a biological therapy and studying its effect in the treatment of cases of SLE may help to displace the use of systemic steroids to avoid their side effects.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

References:

1. **Fairhurst AM, Wandstrat AE, Wakeland EK.** Systemic lupus erythematosus: multiple immunologic phenotypes in a complex genetic disease. Adv Immunol 2006; 92: 1–69.
2. **Rahman A, Isenberg DA.** Systemic lupus erythematosus. N Engl J Med 2008; 358:929-39.
3. **Deng GM, Kyttaris VC, Tsokos GC.** Targeting Syk in Autoimmune Rheumatic Diseases. Front Immunol 2016; 7: 78.
4. **Noble PW, Bernatsky S, Clarke AE, Isenberg DA, Ramsey-Goldman R, Hansen JE:** DNA damaging autoantibodies and cancer: the lupus butterfly theory. Nat Rev Rheumatol 2016; 12: 429-34.
5. **Cerritelli SM, Crouch RJ:** The Balancing Act of Ribonucleotides in DNA. (Trends Biochem Sci 2016; 41: 434-445.

6. **Schmitz J, Owyang A, Oldham E, Song Y, Murphy E, McClanahan TK**, **et al:** IL-33, an interleukin-1-like cytokine that signals via the IL-1 receptor related protein ST2 and induces T helper type 2-associated cytokines. Immunity 2005; 23:479-90.
7. **Pei C, Barbour M, Karen J, Allan D, Mu R, Jiang HR:** Emerging role of interleukin-33 in autoimmune diseases. John Wiley & Sons Ltd, Immunology 2013; 141: 9–17.
8. **Toama A, Kandil H, Mourad H, Soliman1 MI, Esawy AM:** Serum level of Interleukin 33 and its relation with disease activity and clinical presentation in Systemic Lupus Erythematosus. J Clin Exp Dermatol Res 2017; 8: 3.
9. **Hochberg MC:** Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematous. Artheritis Rheum 1997; 40: 1725.
10. **Guo J, Xiang Y, Peng YF, Huang HT, Lan Y, Wei YS:** The association of novel IL-33 polymorphisms with sIL-33 and risk of systemic lupus erythematosus. Molecular Immunology 2016; 1:77:1-7.
11. **Mok MY, Huang FP, Ip WK, Lo Y, Wong FY, Chan EY, et al:** Serum levels of IL-33 and soluble ST2 and their association with disease activity in systemic lupus erythematosus. Rheumatology 2010; 49(3): 520-527.
12. **Wislowska M, Rok M, Stepien K, Kuklo-Kowalska A**: Serum leptin in systemic lupus erythematosus. Rheumatol Int. 2008; 28(5):467-73.
13. **Yang Z, Liang Y, Xi W, Li C, Zhong R:** Association of increased serum IL-33 levels with clinical and laboratory characteristics of systemic lupus erythematosus in Chinese population. Clin Exp Med 2011; 11(2): 75-80.
14. **Li P, Lin W, Zheng X:** IL-33 neutralization suppresses lupus disease inlupus-prone mice. Inflammation 2014; 37 (3): 824–832.