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ORIGINAL ARTICLE

Serum level of interleukin-33 in rheumatoid arthritis patients and its association with bone erosion and interstitial lung disease

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KEYWORDS

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Abstract *Aim of the work:* To analyze the serum levels of IL-33 in RA patients and to investigate its relation to the clinical characteristics, laboratory investigations, joint erosions, functional status and disease activity. Its relation to the presence of interstitial lung disease (ILD) was well thought-out.

Patients and methods: The study included 50 RA patients and 30 matched control. Thorough clinical examination, investigations, disease activity score (DAS-28) and health assessment questionnaire (HAQ) were considered in the patients. Bone erosion was evaluated and interstitial lung disease (ILD) was identified on high-resolution computed tomography. The serum level of IL-33 was measured by enzyme-linked immunosorbent assay.

Results: Serum levels of IL-33 are significantly higher in RA patients (106.96 ± 52.6 pg/ml) than in healthy controls (46.9 ± 23 pg/ml) ($p < 0.001$). A significant correlation was found between IL-33 and the DAS28 ($r = 0.4$, $p = 0.001$), level of rheumatoid factor ($r = 0.45$, $p = 0.001$) and with the presence of ILD ($r = 0.3$, $p = 0.04$). There were no gender differences and the level did not significantly correlate with the age or disease duration. The medications received had no obvious effect on the IL-33 level. The level did not correlate with the HAQ. There was a significant correlation between the CT bone erosion scores the patient's age, disease duration, rheumatoid nodules and DAS28. The erosion score also significantly correlated with the serum IL-33 levels in RA patients ($r = 0.71$, $p = 0.001$).

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Conclusion: These data support the hypothesis that IL-33 may be involved in RA pathogenesis and it may partly contribute to the bone erosion and ILD in RA patients.

1. Introduction

Rheumatoid arthritis (RA) is an autoimmune disease characterized by chronic inflammatory response, including synovial proliferation and excessive proinflammatory cytokine production, leading to eventual cartilage and bone destruction [1]. Several mediators and factors were reported to play a role in Egyptian RA patients including oxidative stress [2–4], T-regulatory cells (Treg) and the imbalance of the Treg/TH17 cytokine axis [5] and cytokines [6,7] have also been implicated in the pathogenic mechanisms of RA. Several proinflammatory cytokines are considered critical in forming the inflammatory process of RA [1]. There has been much evidence confirming the involvement of IL-33 in RA.

Interleukin-33 (IL-33) is a newly reported cytokine of IL-1 family, which has been demonstrated to induce cytokine syntheses and mediate inflammatory responses through its receptor ST2. It is widely expressed in many tissues such as the liver, lung, central nervous system and multiple types of cells including epithelial, endothelial, smooth muscle, macrophages and fibroblasts [8]. Moreover, it is mainly localized in the nucleus but under appropriate signal stimulation such as inflammation, IL-33 is processed and passively released from necrotic cells or actively secreted into the extracellular milieu [9]. Through binding to its receptor ST2, it functions as a proinflammatory cytokine that participates in the development and progression of many diseases including collagen-induced arthritis (CIA) [10], inflammatory bowel disease [11], autoimmune hepatitis, anaphylactic shock [12] and ischemia reperfusion injury [13,14].

It has been reported that administration of sST2 fusion protein dramatically attenuated disease severity by reducing cellular infiltration in the joints, synovial hyperplasia and joint erosion due to inhibiting the release of proinflammatory cytokines comprising IL-6, IL-12, tumor necrosis factor-alpha (TNF-α) and interferon-gamma (IFN-γ). As high expression levels of IL-33 in human RA synovium have been discovered, treatment with an ST2 blocking antibody at disease attenuated the severity of CIA and reduced joint destruction. This highly suggested a critical contribution of locally produced IL-33 to the pathogenesis of joint inflammation and destruction [10].

Interstitial lung disease is a dreaded complication of RA. The most common pattern on high resolution computerized tomography (HRCT) and histopathology is usual interstitial pneumonia (UIP), with nonspecific interstitial pneumonia seen less frequently. Pulmonary function testing most commonly shows reduced diffusion capacity for carbon monoxide and HRCT reveals a combination of reticulation and ground glass abnormalities [15]. Three dimensions computed tomography (3D-CT) is a tomographic imaging method offering high resolution, especially of cortical bone and three dimensional visualization of calcified tissue, allowing clear definition of the margins of erosion. The 3D-CT can provide a clear impression of lesion extent, pattern, shape and proximity to adjacent structures [16].

The aim of the present work was to analyze the serum levels of IL-33 in RA patients and to investigate its relation to the clinical characteristics, laboratory investigations, joint erosions, functional status and disease activity. Its relation to the presence of ILD was well thought-out.

2. Patients and methods

This study was carried out on 50 RA cases diagnosed according to ACR criteria of rheumatoid arthritis [17] were selected from those attending the outpatient Rheumatology clinic of Zagazig University. The patients were 9 males and 41 females, their age ranged from 34 to 69 years with a mean age of 51.1 ± 9.6 years and the duration of the disease ranged from 5 to 23 years with a mean of 11.4 ± 4.9 years. Twenty age and sex matched healthy controls were included. Patients with liver disease, history of anaphylactic shock or ischemia and any other rheumatic disease were excluded. The study was approved by the local ethics committee and consent from the patients was taken before being enrolled in the study.

Full history was taken from the patients, clinical examination performed, disease activity score in 28 joints (DAS28) calculated [18] and function status estimated using the health assessment questionnaire [19]. Laboratory investigations were performed including complete blood count (CBC), Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and Rheumatoid factor (RF). Interleukin-33 (IL-33) was assessed by Enzyme-Linked Immunosorbent Assay (ELISA) in both patients and control.

2.1. Quantitative measurement of IL-33

Human IL-33 PicoKine™ ELISA Kit was used. The assay employs an antibody specific for human IL-33 coated on a 96-well plate. Standards and samples are pipetted into the wells and IL-33 present in a sample is bound by the immobilized antibody. The wells are washed and biotinylated anti-human IL-33 antibody is added. After washing away unbound biotinylated antibody, HRP-conjugated streptavidin is pipetted to the wells. The wells are again washed, a TMB substrate solution is added and color develops in proportion to the amount of IL-33 bound. The Stop solution changes the color from blue to yellow, and the intensity of the color is measured at 450 nm. We calculated the mean absorbance for each set of duplicate standards, controls and samples, and subtracted the average zero standard optical density. The standard curve was plotted on log–log graph paper or by using Sigma plot

Table 1 Demographic, clinical and laboratory characteristics of RA patients and control.

Variable	Patients $n = 50$	Control $n = 30$	p
Age (years)	51.1 ± 9.6 (34–69)	51 ± 9.4(35–69)	0.95
Gender			
Males	12 (24)	7 (23.3)	
Females	38 (76)	23 (76.6)	
Disease duration (years)	11.4 ± 4.9		
Morning stiffness (min)	45 ± 25.5 (5–120)		
DAS28	3.8 ± 1.9		
HAQ (0–3)	1.5 ± 0.7		
CRP (mg/dl)	8.2 ± 14.4	1.7 ± 0.3	**0.04**
ESR (mm/hr)	37 ± 22.5	2 ± 5	**0.001**
RF titre (IU/ml)	>20 (35%)	<15 (67%)	
(<15 = negative)	>60 (55%)	15–30 (33%)	**0.01**
	<15 (10%)		
IL-33 (pg/ml)	106.96 ± 52.6 (25–250)	46.9 ± 23 (15–110)	**<0.001**

DAS28, disease activity score in 28 joints; HAQ, health assessment questionnaire; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor. Bold values are significant at $p < 0.05$. Results are presented as mean ± SD (range) or number (%).

software, with standard concentration on the x-axis and absorbance on the y-axis. The best-fit straight line through the standard points was drawn.

2.2. Computed tomography (CT)

All patients were examined in Radiodiagnosis department (CT unit) in Zagazig University. Toshiba Activion multidetector CT scanner (Toshiba Medical Systems) was used for all examinations.

2.2.1. Three dimension computed tomography (3D-CT) of the wrist

Scan parameters: 90 kV, 100 mA s, pitch 0.4 mm, slice spacing 0.4 mm, overlap 50%. Patients were placed in a prone position with the arm stretched and the palm facing down. Images with a voxel size of $0.4\,mm \times 0.4\,mm \times 1.0\,mm$ were obtained. Erosions on CT images were defined as a sharply demarcated area of focal bone loss seen in two planes, with a cortical break (loss of cortex) seen in at least one plane. CT bone erosions were scored according to Døhn et al. [25]. All wrist bones were assigned a score by the percentage of bone volume involved (score 0–10, by 10% volume increments), leading to a total erosion score for one wrist ranging from 0 to 150. Erosion volume is calculated by software according to the formula: $Vol_{ero} = \Sigma(Area_{ero} \times ST)$, where Vol_{ero} is the erosion volume, $Area_{ero}$ the erosion area on one slice and ST is the slice thickness [20].

2.2.2. Chest high resolution computed tomography

High resolution CT was performed with table speed of 10 mm/s and scan duration of 30 s. Scans were obtained at 120 KVP and 250 mA/s. While patients lying in supine position, scan was performed during full inspiration after the examined patient was instructed to hold breathing.

Statistical analysis: The data are coded and checked to statistical package for social science (SPSS) version 10. The distributions of all variables were examined. Means and standard deviations were calculated for all normally distributed continuous variables. For categorical variables, counts and percentages were calculated. Pearson correlation was used between two variables. The differences of data were evaluated by Student's t-test.

3. Results

The study included 50 RA patients and 30 controls. Demographic, clinical and laboratory characteristics of RA patients and control are presented in Table 1. There was significant difference between patients and control regarding the CRP, ESR and RF titre. There was highly significant increase in the IL-33 level in patients compared to the control ($p < 0.001$).

Fig. 1 presents the bone erosion scores at the wrist region of the hand by 3DCT in the RA patients. Figs. 2 and 3 show the 3DCT erosion of 2 patients. It showed that the most common site of the erosions were the metacarpal bases especially 2nd and 3rd. Most of the erosions were on the radial sides of metacarpal bones. Data are not shown in the controls. There were minimal cortical changes on metacarpals in 9 patients (30%) their ages were above 50 years. The radiological pattern for ILD as detected by HRCT found honey combing (fibrosis) in 26 patients, multifocal peripheral consolidations in 14, mixed pattern in 20 and a ground glass appearance (alveolitis) in 40 patients.

Table 2 shows no significant correlation between IL-33 levels and patients' age or disease durations. There was a significant correlation between IL-33 level and both the DAS 28 ($r = 0.4$, $p = 0.001$) and RF titre ($r = 0.45$, $p = 0.001$). There was no significant correlation of the IL-33 levels with

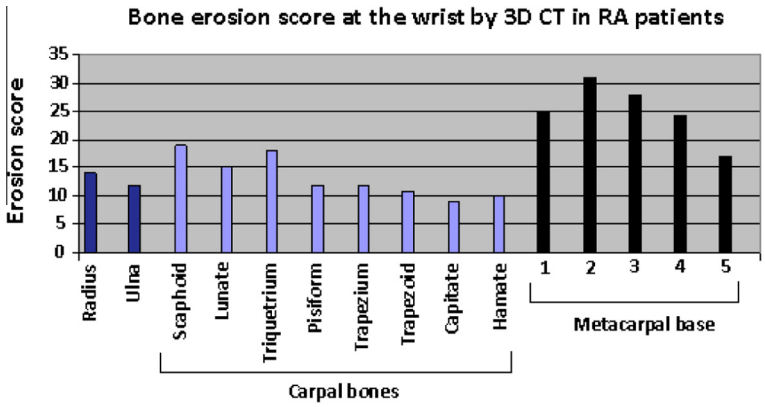

Figure 1 Bone erosion score at the wrist by 3DCT in rheumatoid arthritis patients.

Figure 2 A three dimension computed tomography (3DCT) (oblique view) hand and wrist of a 50 years old rheumatoid arthritis patient with 13 years disease duration. Arrow shows erosion at the MCP base (scored 4) with amalgamation of the carpal bones.

the HAQ or with the treatments ($p > 0.05$). There was a significant correlation between IL-33 and the presence of interstitial fibrosis ($r = 0.3$, $p = 0.04$).

Table 3 shows a significant correlation of CT bone erosion score with the age, disease duration, rheumatoid nodules and DAS28. There was a significant correlation between the CT bone erosion scores and the serum IL-33 levels in RA patients ($r = 0.71$, $p = 0.001$).

4. Discussion

Interleukin-33 is the latest member of IL-1 family. It is broadly expressed in many tissues but is restricted in cellular distribution to smooth muscles, epithelial cells, fibroblasts, dendritic cells and activated macrophage [21]. Recently, evidence has shown that IL-33 contributes to the pathogenesis of RA due to its increasing production of autoimmune inflammatory mediators as proinflammatory cytokines and chemokines [22].

Our study showed increased serum IL-33 in RA patients compared to control which is in agreement with the results of the previous studies [23,24] indicating that it may be involved in the pathogenesis of RA. In this study there were no significant correlation between IL-33 and disease duration which disagrees with the results of Xiangyang and colleagues [25].

There was a significant correlation between IL-33 and RF titre which did not match the results of Mu and colleagues [24] and Xiangyang and colleagues [25]. In this study we showed that there was no significant correlation between IL-33 levels and different type of treatment of RA. We used 3D-CT for a better visualization of the anatomic sites of the joints prone to structural bone damage; we performed a 3-D reconstruction of periarticular bone architecture to search for further cortical bone changes linked to RA. In our study we did not find any significant difference between radiographic scores in males and females. This came in accordance with a study done by Ahlmen and colleagues [26] who found a similar degree of radiographic joint destruction in women compared with men.

In our study erosion scores were strongly correlated with disease duration and age. This erosion scores were also correlated to disease activity in RA patients measured by the DAS28. These results agree with the results of Stach and colleagues [27] who found that erosion scores significantly correlated with DAS28 as a measure of activity in patients. We found significant correlation between radiographic RA scores and RF titre and the presence of nodules. This agreed with the prospective study done by Bukhari and colleagues [28] as they reported that the RF titre, the presence of rheumatoid nodules, and number of swollen joints were significantly correlated to radiographic scores.

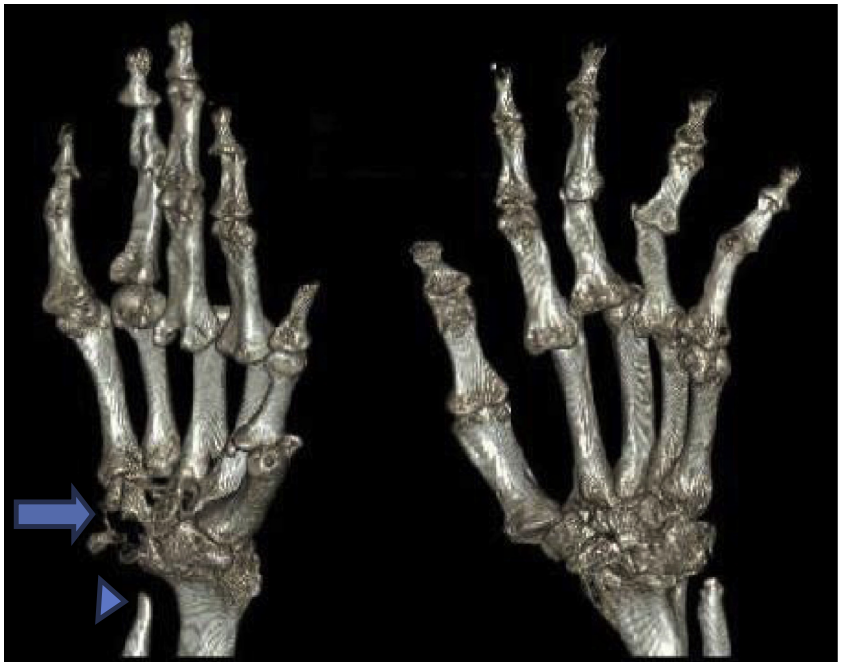

Figure 3 Three dimension computed tomography (3DCT) (posteroanterior view) hand and wrist of a 60 year old rheumatoid arthritis patient with 15 years disease duration. Arrow shows erosion of the carpal bones (scored 4) with amalgamation of the carpal bones. Arrow head shows erosion of the ulna (scored 7).

Table 2 Correlation of serum IL-33 level with various parameters in the rheumatoid arthritis patients.

Serum IL-33 level in RA patients (n = 50)		
Variables	t or r	p
Age (years)	0.2	0.11
Gender	0.54	0.59
Disease duration (years)	0.14	0.5
DAS 28	0.4	**0.001**
HAQ	0.22	0.11
Rheumatoid factor	0.45	**0.001**
Rheumatoid nodules	0.11	0.09
Morning stiffness	0.22	0.09
Interstitial fibrosis	0.3	0.04
Medications		
Methotrexate	1.05	0.29
Corticosteroids	1.04	0.3
Sulfasalazine	0.11	0.9
Antimalarial	0.05	0.95
Azathioprine	1.04	0.95

DAS28, disease activity score in 28 joints; HAQ, health assessment questionnaire. Bold values are significant at $p < 0.05$.

Table 3 Correlation between CT erosion scores with various disease parameters and with IL-33 in rheumatoid arthritis patients.

CT erosion score in RA patients (n = 50)		
Variable	r	p
Age (years)	0.51	**0.01**
Gender	0.06	0.22
Disease duration (years)	0.45	**0.01**
DAS28	0.34	**0.03**
HAQ	0.11	0.09
Rheumatoid factor	0.4	0.05
Rheumatoid nodules	0.44	**0.04**
Morning stiffness	0.11	0.09
Serum IL-33 level	0.71	**0.001**

DAS28, disease activity score in 28 joints; HAQ, health assessment questionnaire. Bold values are significant at $p < 0.05$.

Our study demonstrated a positive correlation between IL-33 levels with DAS28 and the bone erosions score which suggested a role of IL-33 with the disease activity and bone erosions. Bone remodeling is modulated by the immune system and the role of IL-33 in this context has been researched. Mun and colleagues [29] studied the differentiation of osteoclasts from human $CD14^+$ monocytes, which is an osteoclast progenitor. These cells express ST2 on their surfaces, indicating a possible role of IL-33 in this process. IL-33 caused the production of bone resorption factors (c-Src and cathepsin K), showing the differentiation of viable osteoclasts. It is important to note that receptor activator of nuclear factor-kappaB ligand (RANKL) and IL-33 increase the expression of ST2, suggesting positive feedback.

Interstitial lung disease is one of the serious complications of RA. The pathogenesis of ILD in RA patients is unclear. We compared the serum level of IL-33 between RA patients with and without ILD. We found levels of IL-33 to be significantly higher in those with ILD; in this we match the results of Xiangyang and colleagues [25]. Some studies showed that fibrogenesis is strongly linked with the development of T helper type 2, $CD4^+$ T cells. IL-33 plays a role in regulating

Th2 cytokines and leads to increased IL-4, IL-5 and IL-13 expression in vivo. These show that IL-33 is associated with TH2-driven pathology and in-particular those involved in pulmonary fibrosis [30].

In conclusion, this study supports the hypothesis that IL-33 may be involved in RA pathogenesis and it may partly contribute to the bone erosion and ILD found in these patients.

Conflict of interest

None.

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