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Elevated levels of soluble CD14 in serum of patients with systemic lupus erythematosus

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SUMMARY

A soluble form of CD14 (sCD14) was assessed with an ELISA assay in the serum of the following three clinical groups: 35 patients with an inactive phase of systemic lupus erythematosus (SLE), 17 patients with SLE relapses, and 65 normal healthy volunteers. Increased levels of sCD14 were observed in all patients suffering from SLE compared with normal controls. In addition, patients with active SLE revealed higher serum concentrations of sCD14 (median 6·9 mg/*l*) than patients under remission (4·1 mg/*l*; $P < 0{\cdot}0001$). Serum values of sCD14 correlated neither with the number of peripheral blood monocytes bearing the CD14 membrane antigen, nor with serum concentrations of IL-1β. Serum sCD14 was compared with other clinical parameters used to monitor the clinical course of patients with SLE, among them complement C3, anti-dsDNA antibodies and soluble IL-2 receptor (sIL-2R). A good correlation emerged between sCD14 and C3 as well as sIL-2R concentrations, but sCD14 and anti-dsDNA titres disclosed no significant correlation in both groups of patients with SLE. Serial studies in patients with severe SLE showed that serum sCD14 closely parallels the clinical course as defined by an activity score. Our data suggest that serum sCD14 represents a promising parameter to monitor disease activity in patients with SLE.

Keywords systemic lupus erythematosus monocytes soluble CD14 antigen disease activity serum parameters

INTRODUCTION

The monocyte surface antigen CD14 is a glycoprotein with a molecular weight of 53 kD attached to the cell membrane by a glycophosphatidyl-inositol anchor [1,2]. Complementary DNA encoding for this protein has been sequenced and cloned recently [3–5]. CD14 is a myeloid differentiation antigen which is strongly expressed on the monocyte/macrophage lineage. Maturation of monocytes to macrophages is accompanied by an increased expression of CD14 on the cell surface [6]. A soluble form of CD14 (48 kD) has been detected in supernatants of cultured $CD14^+$ cells [7] as well as in serum and urine [8,9]. The biological function of CD14 is not yet clearly understood and is currently under intense investigation. Whereas CD14 was first described as a receptor for lipopolysaccharides [10], more recent data suggest that CD14 is also involved in monocyte–T cell interactions [11]. Most systemic collagen-vascular diseases reveal serological and cellular deficiencies in antigen recognition and processing, where monocytes play a crucial role in concert with T and B lymphocytes. Systemic lupus erythematosus (SLE) is characterized by various aberrant immunoreactions and abnormalities in T and B cell functions [12]. Patients suffering from SLE demonstrate an increased amount of activated T lymphocytes [13]. Under *in vitro* conditions T helper cell activity is enhanced, whereas T suppressor cell function is decreased [14]. Furthermore, patients with SLE show a rise in mutated T cells, indicating a disturbance in the immune surveillance [15]. The exact role of monocytes within this altered cellular network in SLE, however, remains unclear. Nevertheless, monocyte infiltration of organs may potentiate parenchymal lesions and disease progression. Recently, we first described elevated levels of sCD14 in sera of patients with SLE [16]. In the present study patients with different phases of SLE were assessed for sCD14 and compared with a larger collective of normal controls. In addition, to study the predictive role of sCD14 for disease progression, we compared sCD14 values with other serum parameters used to monitor SLE patients, among them complement C3, anti-dsDNA and sIL-2R [17,18]. Moreover, the correlation between IL-1β levels and sCD14 values was determined.

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PATIENTS AND METHODS

Subjects

Blood specimens were obtained from 35 patients with SLE during inactive and from 17 patients during active phases of the

disease. The diagnosis of SLE was determined at least 1 year before start of the study. Disease activity was scored according to the activity index reported by Isenberg *et al.* [19], whereby all patients were classified as having inactive (grade 0–1, corresponding 0–4 points) or active SLE (grade 2–4, > 5 points). The control group consisted of 65 healthy volunteers, all age- and sex-matched. Longitudinal serum specimens from three patients who developed a severe relapse of SLE were assessed retrospectively.

Collection of blood samples

To measure SLE-related serum markers whole blood was collected in serum monovettes (Sarstedt, München, Germany). Samples were allowed to stand for 30 min for clotting and were then centrifuged at 2000 *g*. After immediate determination of C3 values the sera were aliquoted and stored at −20°C for further use.

Monocytes were assayed in EDTA plasma using a Coulter counter S-plus IV unit (Coulter Electronics Inc., Hialeah, FL). In addition, monocytes were counted manually in stained blood smears.

ELISA for sCD14, sIL-2 receptor and IL-1β

sCD14 was measured with a sandwich ELISA using two MoAbs against CD14 (IBL, Hamburg, Germany). In brief, serum specimens were diluted 1:200 in PBS and incubated for 1 h at room temperature in a microtitre plate precoated with the murine anti-CD14 MoAb. The plates were washed three times and a second anti-CD14 antibody conjugated with horseradish peroxidase (HRP) was added. After colour development for 5–10 min the reaction was stopped with H_2SO_4 and the plates were read at 490 nm using a microtitre plate reader (Titertek Multiscan, Flow, Meckenheim, Germany). Intra- and interassay variance was 11% and 15%, respectively.

Soluble IL-2 receptor was measured with a sandwich ELISA (T-Cell Science, Cambridge, MA) according to the manufacturer's manual. Normal values in healthy persons were 530 U/ml (median) in our laboratory.

IL-1β was determined with a sandwich ELISA from Immunotec (Dianova, Hamburg, Germany). In this ELISA an acetylcholinesterase-conjugated MoAb against IL-1β was used for colour development. Determination of normal serum concentrations revealed a median level of 38 pg/ml. However, scattering of IL-1β concentrations in serum samples from normal controls was rather high (min. 0 pg/ml, max. 570 pg/ml).

Anti-dsDNA and antinuclear antibody levels

Autoantibodies to dsDNA were measured with a quantitative ELISA (Orgasan, Mainz, Germany). The assay was performed according to the manufacturer's manual. Results of anti-dsDNA values were expressed in U/ml using the WHO reference preparation Wo/80 as an ultimate standard. Normal concentrations of dsDNA antibodies in our laboratory were below 25 U/ml, and a significant rise was defined for values exceeding 40 U/ml. Anti-nuclear antibodies (ANA) in patient serum specimens were measured with an immunofluorescence test using slides coated with epithelial cells and fibroblasts of human origin (ANA HEp2 immunoassay; Freka-Fluor, Fresenius, Germany). Test calibration was performed using the WHO standard reference serum preparation no. 66/233.

Serum complement C3 concentration

Serum C3 was determined immediately after blood sampling using a Behring automated nephelometric analyser. Intra- and interassay variance were both below 12%. Normal C3 values based on determinations from 65 healthy persons (32 women, 33 men) were 65 ± 9·7 mg/dl (median 64·6 mg/dl).

Statistical analysis

All statistical analyses were performed with a software package BIAS, version 3·0, established by Dr Hanns Ackermann, Department of Biomathematics, University of Frankfurt am Main. Differences in parameters between two groups were evaluated with the Mann–Whitney *U*-test. Spearman's rank correlation test was applied to evaluate possible correlations between different study parameters within a group. $P < 0{\cdot}05$ was considered significant.

RESULTS

Soluble CD14 in healthy subjects and patients with SLE

Serum levels of sCD14 in normal healthy subjects ($n = 65$, mean age 37 ± 11 years) were found to be 2·18 ± 0·46 mg/*l* (median 2·1 mg/*l*), without any significant differences between males and females.

A significant rise in serum sCD14 concentrations was found in the group of patients with SLE. In clinically and serologically inactive SLE sCD14 increased to 4·1 ± 0·78 mg/*l* (median 4·1 mg/*l*), with a significance of $P < 0{\cdot}0001$ compared with healthy controls. In patients suffering from an active phase of SLE sCD14 was elevated even further to 7·1 ± 1·9 mg/*l* (median 6·9 mg/*l*), with a significance of $P < 0{\cdot}0001$ *versus* the inactive SLE group of patients (Fig. 1). Serum sCD14 values and the number of peripheral blood monocytes did not correlate (r_s: −0·086; $P = 0{\cdot}617$). Serum creatinine of patients with active and inactive SLE did not differ significantly from normal controls ($P > 0{\cdot}1$). sCD14 values and serum creatinine concentrations did not correlate.

ANA, anti-dsDNA antibodies and complement C3

All patients with SLE were positive for ANA. Values ranged from 243 ± 385/titre in the inactive and from 305 ± 335/titre in the active SLE group. Anti-dsDNA antibody levels rose

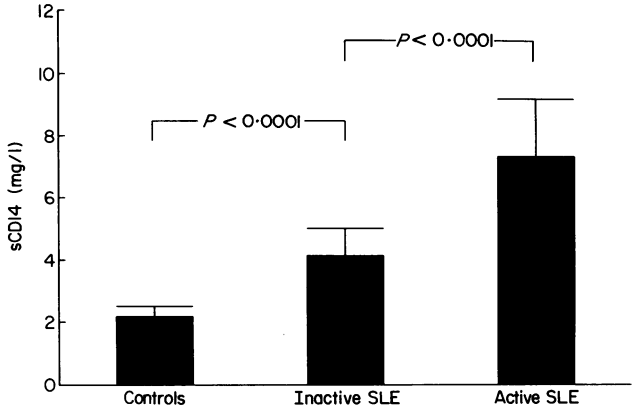

Fig. 1. Soluble CD14 (sCD14) concentrations in sera of patients with systemic lupus erythematosus (SLE) and healthy controls. Statistical analysis was performed according to the Mann–Whitney *U*-test.

significantly in patients with an exacerbation of SLE (Table 1), while serum C3 levels decreased compared with normal controls as well as with patients with inactive phases of SLE.

Soluble IL-2 receptor and IL-1β

During remission phases of SLE sIL-2R values were not significantly different from normal control persons. However, a significant increase in sIL-2R serum concentrations in patients with active SLE became apparent (Table 1). Serum levels of IL-1β varied widely, with a tendency toward higher values in the group of patients with an active form of SLE. No correlation of serum IL-1β values with clinical signs of the disease (arthralgias, vasculitis, proteinuria, leucopenia, thrombocytopenia) could be observed.

Relationship between sCD14 and other parameters

Serum sCD14 concentrations in SLE patients were assessed to elucidate a possible association with disease activity scores and possible correlations with other serological parameters (Table 2). The data obtained reveal an excellent correlation of sCD14 values with disease activity as calculated using the score introduced by Isenberg *et al.* [19]. In addition, a significant correlation was found between the decrease in serum C3 and the rise in sIL-2R values. However, serum levels of anti-dsDNA antibodies and IL-1β concentrations did not correlate with serum sCD14 in either group of patients.

Serum sCD14 in SLE patients: longitudinal studies

In three patients, women 21, 28 and 42 years old suffering from a severe SLE relapse with kidney involvement (glomerular proteinuria, microhaematuria, cast formation), sCD14 was monitored for more than 18 months. One clinical follow up, which is also representative for the other two patients, is shown in Fig. 2a,b. sCD14 values closely parallel the altered disease activity score, sIL-2 receptor values and changes in the immunosuppressive treatment. As revealed by serial measurements during a moderately active phase of SLE until the end of November 1991, anti-dsDNA antibody levels, sIL-2R and sCD14 concentrations were initially high. Subsequently IL-2R and anti-dsDNA decreased, while sCD14 values remained constant. Coincidentally with a clinical exacerbation of the SLE in December 1991 presenting as skin rash, hypertension, coughing, an unselective pattern of glomerular proteinuria and microhaematuria, sIL-2R levels rose whereas anti-dsDNA values did not increase further. In spite of the clinical relapse, serum levels of C3 increased continuously from October 91 until the end of 1992. Initiation of a more aggressive immunosuppressive regimen with intermittent pulse doses of cyclophosphamide was accompanied by a continuous decline of sCD14, sIL-2R and anti-dsDNA antibody values. Correspondingly, the clinical activity score improved from 10 to 2. Proteinuria in the nephrotic range as a result of the SLE exacerbation continued, however.

Table 1. Comparison between serum levels of anti-dsDNA, sIL-2R, IL-1β and C3 in patients with active and inactive forms of systemic lupus erythematosus (SLE)

	Anti-dsDNA (U/ml)	sIL-2R (U/ml)	IL-1β (pg/ml)	C3 (mg/dl)
Inactive SLE	95±114	620±430	395±624	63·4±15·1
$n=35$	(53)	(523)	(49)	(60)
Active SLE	298±348	1294±523	507±1291	34·9±13·6
$n=17$	(227)	(1238)	(95)	(31·5)
P*	0·048	0·001	NS	<0·0001

* Spearman's rank sum test.

Values are mean±s.e.m., with median in parentheses. NS, Not significant.

Table 2. Correlation coefficients* between serum levels of sCD14 and the score of disease activity index†, levels of complement C3, anti-dsDNA, sIL-2R and IL-1β in systemic lupus erythematosus (SLE)

	Disease activity	Complement C3	Anti-dsDNA	sIL-2R	IL-1β
r	0·66	−0·39	0·24	0·47	0·05
P	<0·0001	0·0075	NS	0·003	NS

NS, Not significant.

* Spearman's rank sum test.

† Disease activity index according to Isenberg *et al.* [19].

DISCUSSION

The present study was conducted to elucidate the potential usefulness of a soluble membrane antigen from monocytes (sCD14) in sera of patients with SLE. Serum levels of sCD14 were compared with those of anti-dsDNA antibodies, IL-1β, C3, and sIL-2R. To our knowledge serial changes of sCD14 during the course of SLE have not previously been described. Using an ELISA for sCD14 we showed a significant rise in the monocytic antigen in sera of SLE patients. Specifically, more elevated levels were found during active than during inactive phases of the disease as defined by clinical and serological criteria. Patients suffering from SLE may benefit from such a parameter which can indicate early signs of disease activity and immune activation. In addition to clinical criteria ('activity score'), anti-dsDNA antibody titres, complement C3, acute phase reactants, cryoglobulins, circulating immune complexes, and sIL-2R represent some of the serum parameters used to assess disease activity [20]. At present it appears that clinical signs of disease activity [19] as well as the determination of serological markers ensure efficient monitoring of patients with SLE [21]. In our study patients with active SLE exhibited higher levels of soluble IL-2R, which is released by activated lymphocytes, as well as augmented sCD14 values. Previous studies reported elevated levels of sIL-2R in patients with SLE which were additionally associated with high anti-dsDNA antibody titres, the existence of cryoglobulins, the presence of proteinuria, and a high degree of spontaneous IgG secretion from peripheral blood lymphocytes [22,23]. However, in contrast to such cross-sectional evaluations, a longitudinal study showed that sIL-2R levels do not always parallel other serological markers such as anti-dsDNA antibody titres, indicating that disease activity in SLE may be expressed in different, partially discordant facets of immunomodulation [24]. The goal in SLE diagnosis and follow up is to define parameters which change significantly before the onset of clinically apparent signs of disease activity. So far, complement C3 has been the best

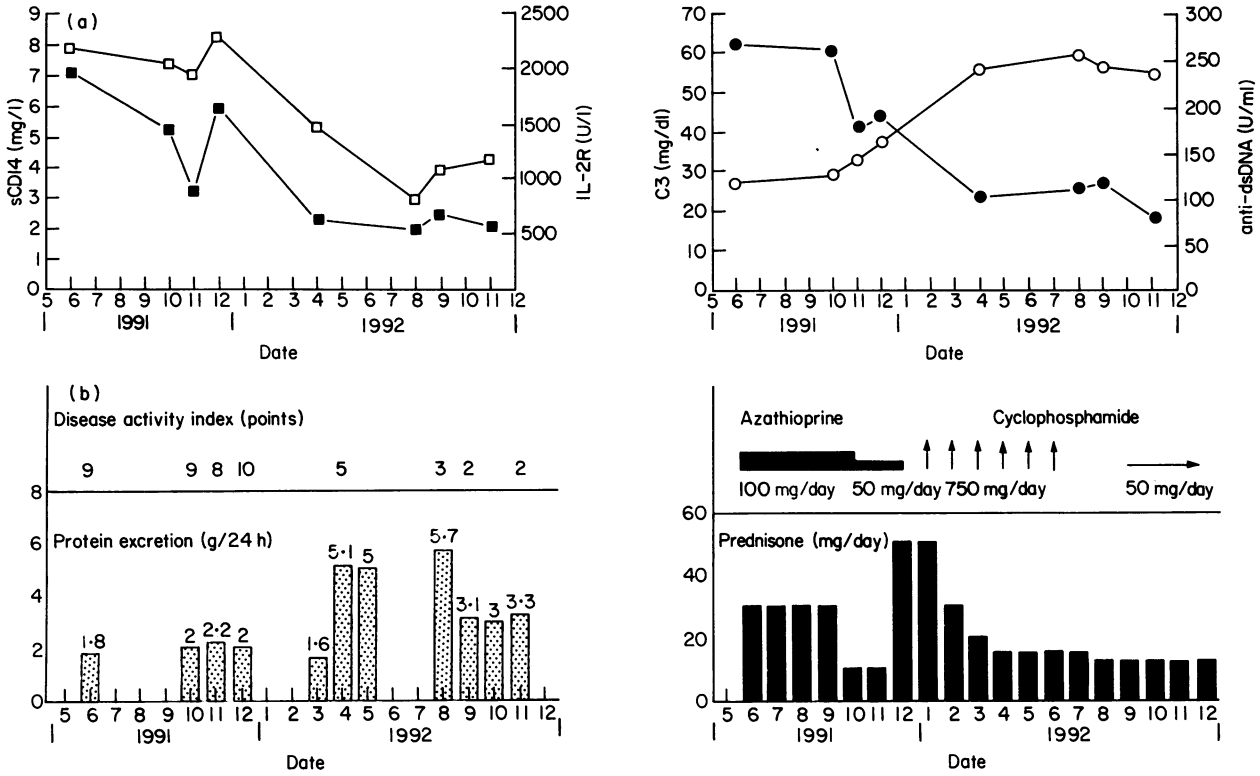

Fig. 2. (a) Time course of serum parameters sCD14, sIL-2R, C3 and anti-dsDNA before, during and after a major exacerbation in a female suffering from severe systemic lupus erythematosus (SLE). (b) Clinical data and immunosuppressive treatment of the patient with systemic lupus erythematosus as shown in a. □, sCD14; ■, IL-2R; ○, C3; ●, anti-ds DNA.

documented serum marker for SLE, with a well known decrease in active phases of the disease [25]. On the other hand, in inactive phases serum C3 shows no significant changes compared with normal controls, whereas sCD14 is already elevated.

The role of monocytes in the pathogenesis of SLE is not yet clear. Monocytes of patients suffering from SLE have markedly reduced phagocytic activity compared with normal controls [26]. The release of cytokines and other immunoregulatory factors from monocytes is altered in SLE: after stimulation with *Escherichia coli* lipopolysaccharide or phorbol myristate acetate (PMA), monocytes from SLE patients are deficient in the production of IL-1β [27]. Since IL-1β is a multipotent cytokine initiating and amplifying T cell-dependent immune responses, diminished production of IL-1β provides evidence for the participation of monocytes in the immunoregulatory defect in SLE. On the other hand, in our study the IL-1β plasma levels in SLE patients showed no significant differences between active and inactive phases of the disease. In both of the groups the IL-1β values differed widely, and no relationship between IL-1β and clinical symptoms could be found. Furthermore, the Fc receptor function may be defective in SLE. Monocytes under these pathological conditions demonstrate a reduced avidity for and decreased degradation of heat-aggregated IgG [28]. In addition to the reduced number of Fc receptors, the expression of other monocyte surface molecules is also impaired in SLE: an increased number of $CD23^+$ monocytes [29] and a decline in $HLA\text{-}DR^+$ monocytes have been reported in patients with clinical relapses [30]. T cell-derived IL-4 up-regulates the expression of HLA-DR [31] and down-regulates CD14 expression [32]. Moreover, IL-4 apparently blocks the release of sCD14 in monocytes [33]. Decreased expression of HLA-DR antigens and increased sCD14 concentrations in SLE may thus be due to the same pathogenic mechanism, a diminished production of IL-4 by activated T cells resulting in an imbalance in the immunoregulatory network. We failed to detect any IL-4 activity in sera of SLE patients and normal individuals (data not shown), however, but this does not exclude locally restricted synthesis and para-juxtacrine action of the lymphokine.

Recently, CD14 was recognized as an important regulatory molecule in monocyte–T cell interactions [11]. T cells activated via the TCR/CD3 complex failed to proliferate in the presence of monocytes preincubated with an anti-CD14 MoAb. Activation of the TCR–CD3 complex apparently plays a role in the pathogenesis of SLE, since T cells from SLE patients show an enhanced proliferative response when stimulated via the CD3 pathway [34]. The exact function of CD14 within the immunological network, however, remains to be established. Nevertheless, the increase in serum sCD14 in SLE supports the hypothesis that monocytes may contribute to the disease, especially since both active and inactive phases of SLE exhibit increased sCD14 serum levels compared with normal controls. Our results demonstrate that sCD14 is a useful complementary marker for monitoring patients with SLE. We are currently investigating the release of sCD14 in supernatants of cultured monocytes and peripheral blood mononuclear cells (PBMC) from normal persons and patients with SLE in order to gain a better insight into the impact of monocytes on various activity phases of the disease.

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