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Cytokine Profile in Systemic Lupus Erythematosus, Rheumatoid Arthritis, and Other Rheumatic Diseases

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We investigated serum levels of interleukin-6 (IL-6), interferon-gamma (IFN-γ), and tumor necrosis factor alpha (TNFα) from patients with systemic lupus erythematosus (SLE) and its various clinical manifestations of disease and from patients with rheumatoid arthritis (RA) and other rheumatic diseases. The serum levels of IL-6 and IFN-γ were highly elevated from patients with SLE associated with lymphadenopathy (LN) or nephrotic syndrome (NS). On the contrary, the serum levels of TNFα were elevated from most patients with SLE associated with thrombocytopenia (TP). However, serum levels of TNFα were in the normal range from patients with SLE associated with NS, LN, or central nervous system disease. Of interest, patients with SLE associated with humoral immunodeficiency disorder, hypogammaglobulinemia, had highly elevated levels of serum IL-6. The concanavalin A-stimulated mononuclear cells (MNC) of patients with SLE associated with TP secreted highly elevated levels of TNFα compared to other patient groups. We suggest that abnormal production of various cytokines in SLE is an intrinsic defect of MNC and the immune system that may be the key element for a variety of clinical manifestations of this disease.

KEY WORDS: Systemic lupus erythematosus; rheumatoid arthritis, interleukin-6; interferon gamma; tumor necrosis factor alpha.

INTRODUCTION

Cytokines are considered to be the most important secretions of the immune system that participate in a variety of cellular, inflammatory and pathogenic processes in human disease (1–3). Cytokines that are produced in large amounts and gain access to the circulation act in a hormonal fashion and have drastic effect on other cells. Therefore, the excessive or insufficient production of certain cytokines may contribute to the pathogenicity of certain diseases (1, 2, 4–9). The recent availability of recombinant cytokines has been foremost in establishing their individual activities; in addition, monoclonal antibodies (mAb) directed against individual factors have facilitated purification and improved the specificity of bioassays for individual cytokines. Among the many cytokines, interleukin-1 (IL-1), IL-2, IL-6, interferon gamma (IFN-γ), and tumor necrosis factor alpha (TNFα) are the well-characterized multifunctional cytokines, important in the regulation of immune response, hematopoiesis, acute-phase reactions, and inflammation of certain immune disorders (1–3, 8–9). There is increasing evidence of cytokine abnormalities in several autoimmune diseases and, in particular, in rheumatic diseases (10, 11).

Systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) continue to be the widely recognized rheumatic diseases of unknown etiology in which extensive immune dysfunction has been reported (12–20). We recently demonstrated highly elevated secretion of soluble IL-2 receptor (sIL-2R) levels in serum of patients with SLE and thrombocytopenia (21). Since imbalances of the cytokine network in autoimmune disease may be detrimental for the severity or clinical manifestations of the disease, we quantified several cytokines (IL-6, IFN-γ, and TNFα) from serum samples, and their *in vitro* production by blood mononuclear cells was determined for patients with SLE and RA.

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MATERIALS AND METHODS

Patients

Patients (all Saudi women) with definite SLE as defined by the American Rheumatism Association (ARA) 1982 revised criteria (22), who attended the Rheumatology Clinic at the Asir Central Hospital, Abha, and King Khalid Hospital, Riyadh, were investigated. Patients with active SLE (all of them females, 18–43 years old) had malar rash, photosensitivity (most of the patients), fever, polyarthritis (all of them), serositis (some), alopecia (19 patients), an elevated erythrocyte sedimentation rate (ESR) (some; ESR ≥42 mm/hr), a high antinuclear antibody (ANA) (all of them) and anti-nDNA titer (all of them; ≥1:640) as determined by indirect-immunofluorescence technique (Electronucleonics, Inc., Bethesda, MD), and low C3 (16–61 mg/dl) and C4 (11–43 mg/dl) (21). Patients with active SLE and NS (nephrotic syndrome) had massive proteinuria >3.5 g/24 hr and heavy albuminuria leading to hypoalbuminemia. Patients with active SLE and TP (thrombocytopenia) had a platelet counts in the range of 18,000 to 53,000/mm^3. Patients with active SLE and CNS (central nervous system disease) had additional clinical signs which included headache (four patients), nervousness (all of them), psychosis (all of them), aphasia (four patients), memory disturbances and blurred vision (six patients), and seizures (seven patients); only these patients managed to have EEG. Five of them had focal activities. The EEG of three patients with CNS was not available. Patients with active SLE and LN (lymphadenopathy) had enlarged cervical, inguinal, and axillary (some) lymph nodes. Histopathology of the biopsied lymph node showed necrosis and reactive hyperplasia without malignant change. The patients with active SLE–LN had polyarthritis (all of them), photosensitivity (five of them), fever (three of them), malar rash (all of them), elevated ANA and anti-nDNA titers (≥1:640), and low C3 (6–18 mg/dl) and C4 (3–14 mg/dl).

Patients with inactive SLE were those who were considered in clinical remission and had been treated with prednisolone but had not received it for at least 1 month before our study. They had none of the above clinical features of the active disease but had ANA and anti-nDNA titers of 1:20 to 1:80 and almost-normal levels of C3 (53–98 mg/dl) and C4 (31–67 mg/dl).

Patients with RA (13 males and 18 females, 28–56 years old) fulfilled the ARA criteria (23). Patients with BD (Behcet's disease) (eight males and three females; 23–37 years old) had active signs and symptoms (painful oral ulcers, painful genital ulcers, iritis, some skin lesions, such as erythema nodosum folliculitis), and laboratory findings (elevated ESR and positive c-reactive protein). Patients with SS (Sjogren's syndrome) (seven males and two females, 28–41 years old) were diagnosed based on the presence of keratoconjunctivitis sicca, xerostomia, a positive salivary gland biopsy showing mononuclear cell infiltrates, and the absence of an associated connective tissue disease (24). Patients with PMR (polymyalgia rheumatica) (10 males and 4 females, 31–47 years old) fulfilled the diagnostic criteria proposed by Bird *et al.* (25). Patients with active SLE, RA, BD, SS, and PMR were investigated before the start of any form of immunosuppressive therapy, although some were taking nonsteroidal antiinflammatory drugs.

Fourteen patients (11 males and 3 females, 42 ± 6 years old) with an established history of NS proved by renal biopsy and low levels of serum albumin (19–28 g/L) and total protein (43–58 g/L) but elevated urinary albumin (4.2–7.6 g/day) and total protein (5.2–9.6 g/day) and 15 patients (9 males and 6 females, 39 ± 5 years old) with TP characterized by consistently low platelet counts (below 61,000/mm^3) were investigated. Patients with NS and TP had no other disease. The healthy controls were between 18 and 54 years old (38 males and 12 females).

Cytokine Production

Peripheral blood mononuclear cells (MNC) were isolated by Histopaque-1077 (Sigma Chemical Co., St. Louis, MO) density-gradient centrifugation (15). MNC (1×10^6 cells/ml) were cultured in RPMI-1640 medium (Flow Laboratories, UK) with and without concanavalin A (Con A; 5 μg/ml) for a total period of 48 hr in a humidified incubator at 37°C and 5% CO_2. The supernatants obtained were filtered, stored at −70°C, and assayed for concentrations of cytokines.

IL-2 Activity

IL-2 activity from the Con A-stimulated MNC supernatants was measured in a standard proliferation assay (incorporation of ^{3}H-thymidine) using an

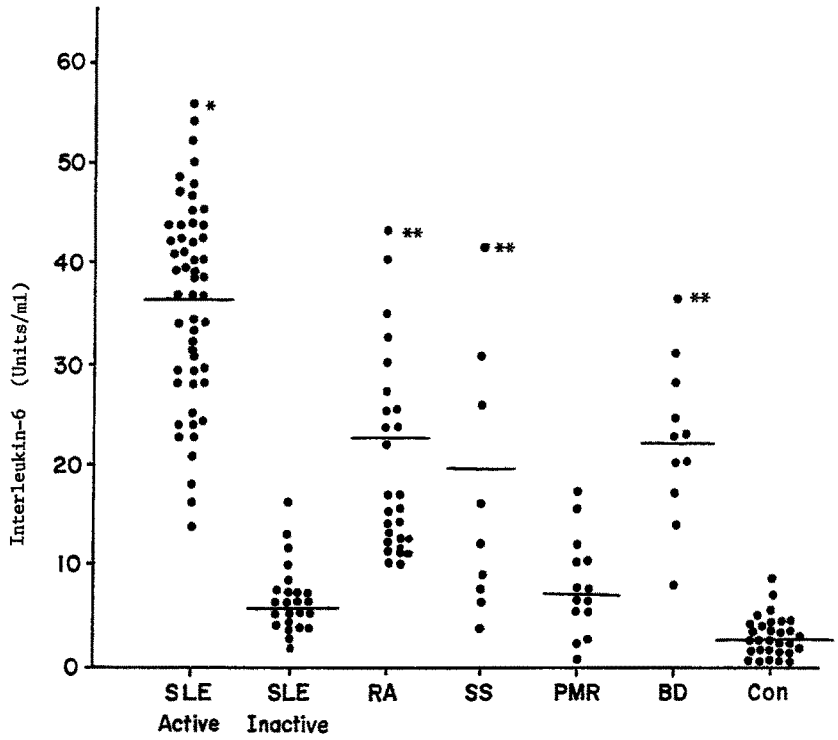

Fig. 1. Serum levels of IL-6 in patients with active SLE (N = 53), inactive SLE (N = 25), RA (N = 31), SS (N = 9), PMR (N = 14), and BD (N = 11) and normal controls (Con; N = 50). Horizontal lines represent the mean. N = number of patient samples analyzed. (*)P <0.001 versus inactive SLE and PMR patients and normal controls. (**)P <0.001 versus normal controls.

IL-2-dependent CTLL cell line described earlier (15, 26). Recombinant human IL-2 was used as a standard to quantitate the amount of IL-2 present.

IL-6 Activity

IL-6 activity from serum samples and Con A-stimulated MNC supernatants was determined by a solid-phase enzyme-linked immunosorbent assay (ELISA) based on the antibody sandwich principle, using an Inter Test-6 ELISA kit purchased from Genzyme (Boston, MA). The assay was standardized against recombinant human IL-6. We have determined that the quantitation of IL-6 by commercially available ELISA kit (Genzyme) gives almost identical results compared with the bioassay procedure using the IL-6-responsive murine hybridoma cell line MH60-BSF2 (kindly provided by T. Kishimoto, Institute for Molecular and Cellular Biology, Osaka University, Osaka, Japan).

IFN-γ Activity

IFN-γ was assayed in a solid-phase sandwich ELISA developed in our laboratory. In brief, microtiter plates (Nunc, Immunotype II) were coated overnight with mAbs to IFN-γ (Genzyme) in carbonate buffer, pH 9.6. After washing and blocking with bovine serum albumin, samples and standards (recombinant human IFN-γ; Genzyme) were incubated for 2 hr at 37°C. Plates were washed and a second antibody, rabbit anti-IFN-γ, was incubated for 2 hr. After washing and adding alkaline phosphatase-conjugated goat antibody to rabbit IgG (Sigma Chemical Co., St. Louis, MO), the color developed with the *p*-nitrophenyl phosphate was read at 405 nm in an ELISA plate reader with known standards.

TNFα Activity

The concentration of TNFα from the serum samples and in the Con A-stimulated MNC culture

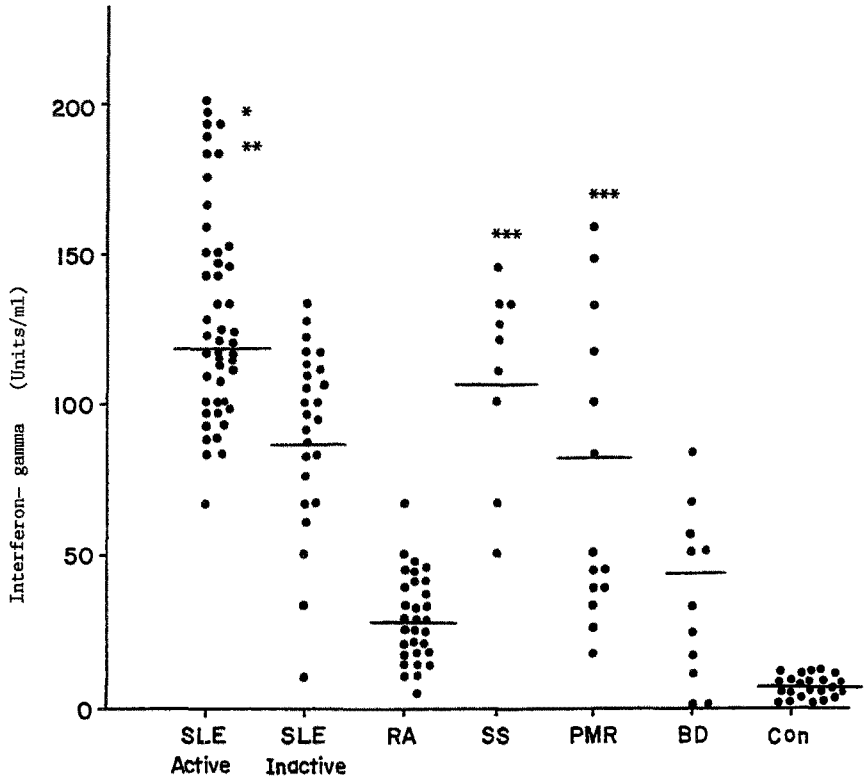

Fig. 2. Serum levels of IFN-γ in patients with active SLE (N = 53), inactive SLE (N = 25), RA (N = 31), SS (N = 9), PMR, (N = 14), and BD (N = 11) and normal controls (Con; N = 30). (*)P <0.001 versus RA patients and normal controls. (**)P <0.01 versus inactive SLE patients. (***)P <0.001 versus normal controls.

supernatants was assayed by an ELISA using two mAbs recognizing different epitopes of TNFα (Genzyme, Boston, MA) according to the standard technique (27). In this assay, no cross-reactivity was observed with IL-1, IL-2, IL-6, or IFN-γ. The assay was standardized against human recombinant TNFα. The limit of the assay way 10 pg/ml. TNFα activity was totally inhibited by anti-TNF neutralizing antibody.

Cytokine values from serum samples and Con A-stimulated MNC are expressed as the mean of triplicate determinations for each sample.

RESULTS

The serum levels of IL-6, IFN-γ, and TNFα cytokines from patients with SLE (active and inactive disease), RA, SS, PMR, and BD and normal controls are given in Figs. 1–3.

As shown in Fig. 1, the serum IL-6 levels were high in most patients with active SLE, RA, SS, and BD compared to normal controls. But serum levels of IL-6 were low in most patients with inactive SLE and PMR. The serum levels of IFN-γ were elevated from both active and inactive SLE patients and from most patients with SS and PMR (Fig. 2). On the contrary, most patients with RA and BD demonstrated low levels of serum IFN-γ. Of interest, however, serum levels of TNFα were elevated in 13 of 53 active SLE, 2 of 31 RA, and 3 of 11 BD patients, but were almost in the normal range in inactive SLE, SS, and PMR patients (Fig. 3).

SLE is a multisystem disease, and occasionally patients with active SLE have NS, TP, CNS involvement, and LN. We separated active SLE patients strictly according to other additional clinical manifestation of the disease, i.e., NS, TP, CNS disease, or LN (21). To evaluate the possible associations between cytokine levels (IL-6, IFN-γ, and TNFα) and other clinical manifestations of the disease, serum levels of these cytokines were measured from patients with active SLE associated with either NS, TP, CNS, or LN. Patients with NS and TP but without SLE were also included for comparisons, in addition to normal controls (Fig. 4–6). As shown in Fig. 4, the levels of serum IL-6

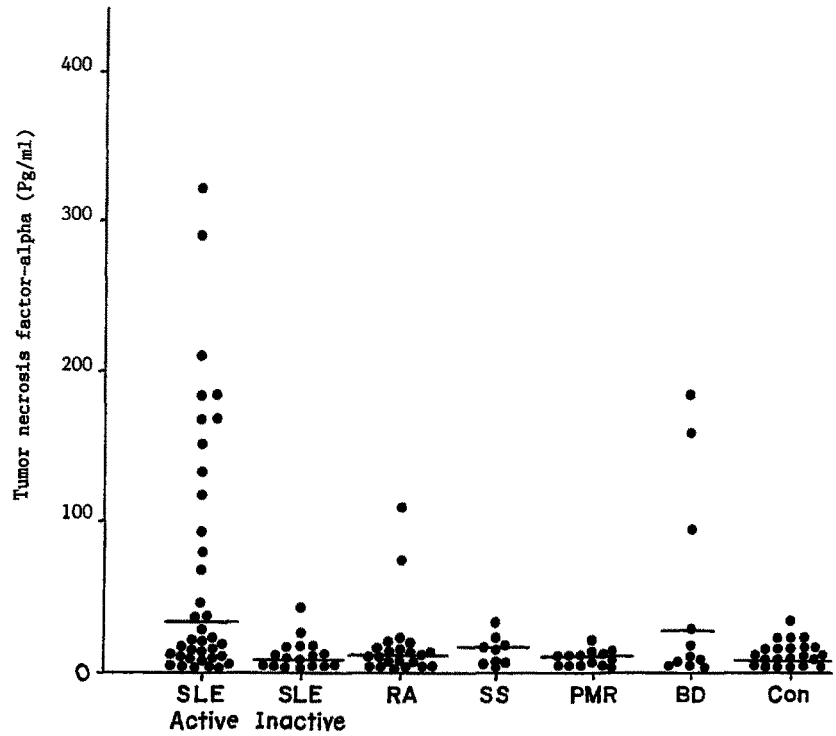

Fig. 3. Serum levels of TNFα in patients with active SLE (N = 53), inactive SLE (N = 25), RA (N = 31), SS (N = 9), PMR (N = 14), and BD (N = 11) and normal controls (Con; N = 50).

were highly elevated in all seven patients with active SLE and LN. Patients with active SLE associated with NS also had elevated levels of serum IL-6 compared to patients with TP or CNS disease. Most patients with SLE associated with TP or CNS had almost-equal levels of serum IL-6 activity.

The serum levels of IFN-γ measured in these subsets of active SLE patients and controls are shown in Fig. 5. Similarly, the serum levels of IFN-γ were also high in all patients with active SLE associated with LN. Patients with active SLE associated with NS also demonstrated elevated levels of serum IFN-γ compared to other patient groups and controls. The data shown in Figs. 4 and 5 revealed that almost-equal levels of IL-6 and IFN-γ were secreted in serum of patients with active SLE associated with LN or NS and other patient groups.

The serum levels of TNFα were increased only in patients with active SLE associated with TP (Fig. 6). Patients with active SLE associated with NS, CNS, or LN had near-normal levels of serum TNFα. However, some patients with TP but without SLE also had slightly elevated levels of TNFα compared to the normal controls.

Immunodeficiency disorders have occasionally been observed in some patients with SLE. Selective IgA deficiency and complement C4 deficiency are the most common findings in some patients with SLE (28–30). During our investigations of active SLE disease between 1986 and 1990, we identified a few patients with active SLE with either hypogammaglobulinemia, selective IgA deficiency, or C4 complement deficiency disorders. The serum samples of these active SLE patients stored at −70°C and examined for immunoglobulin levels (IgG, IgA, and IgM), C3 and C4 complement levels, and IL-6, IFN-γ, and TNFα cytokines are given in Table I. As can be seen, patients with SLE associated with hypogammaglobulinemia had elevated levels of IL-6. However, the serum levels of these cytokines varied case by case in various SLE groups. No clear correlation existed between these immunodeficiency disorders in SLE and serum IL-6, IFN-γ, or TNFα cytokine secretions.

Con A-induced production of IL-2, IL-6, IFN-γ, and TNFα by MNC from patients with SLE and RA and normal controls is given in Table II. Spontaneous IL-2, IL-6, IFN-γ, and TNFα production by MNC incubated with medium alone was rare. As

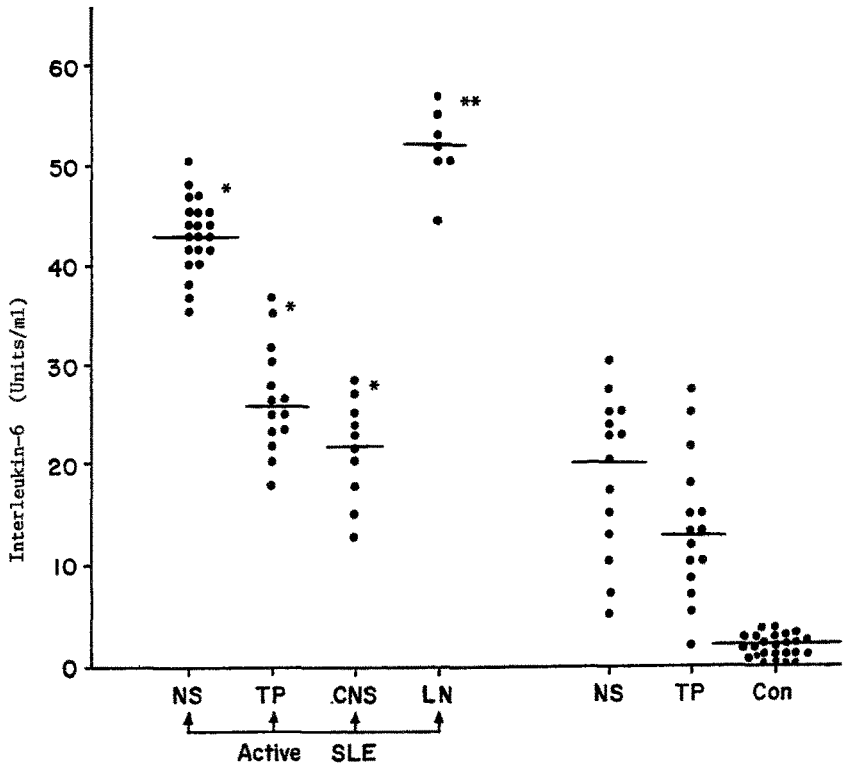

Fig. 4. Serum levels of IL-6 in patients with active SLE associated either with NS (N = 21), TP (N = 14), CNS (N = 10), or LN (N = 7) and in patients without SLE but with NS (N = 14) or with TP (N = 15) and normal controls (Con; N = 30). (*)P <0.001 and (**)P <0.0001 versus normal controls.

shown, IL-2 production by Con A-stimulated MNC was markedly diminished in patients with active SLE associated with NS, LN, or TP compared to patients with RA and normal controls. However, IL-2 activity was also lower in RA than normal controls. IL-6 production by MNC of patients with SLE associated with LN or NS was considerably higher than patients with SLE and TP or from RA. However, MNC from patients with SLE associated with LN produced significantly elevated levels of IFN-γ compared with other patient groups and controls. Con A-induced TNFα production by MNC is also shown in Table II. TNFα production was in the normal range in patients with SLE associated with NS or LN and in RA patients. Of interest, however, Con A-induced MNC of patients with SLE associated with TP produced significantly higher amounts of TNFα compared to other patient groups and controls.

DISCUSSION

Within the complex immunoregulatory network in SLE, RA, and other immunologically mediated diseases, IL-1, IL-2, IL-6, IFN-γ, and TNFα cytokines secreted by the abnormal immune system are thought to be of particular importance because of their potential role in inflammation as well as in host defence mechanisms. Previous studies have demonstrated defective IL-1 and IL-2 synthesis by MNC of patients with SLE (34). This study examines the levels of circulating IL-6, IFN-γ, and TNFα in patients with SLE associated with different clinical manifestations of disease and in patients with RA and other rheumatic diseases. Our main finding is that serum levels of IL-6 and IFN-γ are highly elevated in a subset of patients with SLE associated with NS or LN. However, serum levels of TNFα are elevated in most patients with SLE associated with TP. Additionally, the data show that active SLE patients with humoral immunodeficiency disorder, such as hypogammaglobulinemia, also have highly elevated levels of serum IL-6. On the contrary, no correlation was observed in patients with SLE associated with hypogammaglobulinemia, selective IgA deficiency, or C4 complement deficiency disorders with regard to secretion of other cytokines. Of interest, however, serum levels of

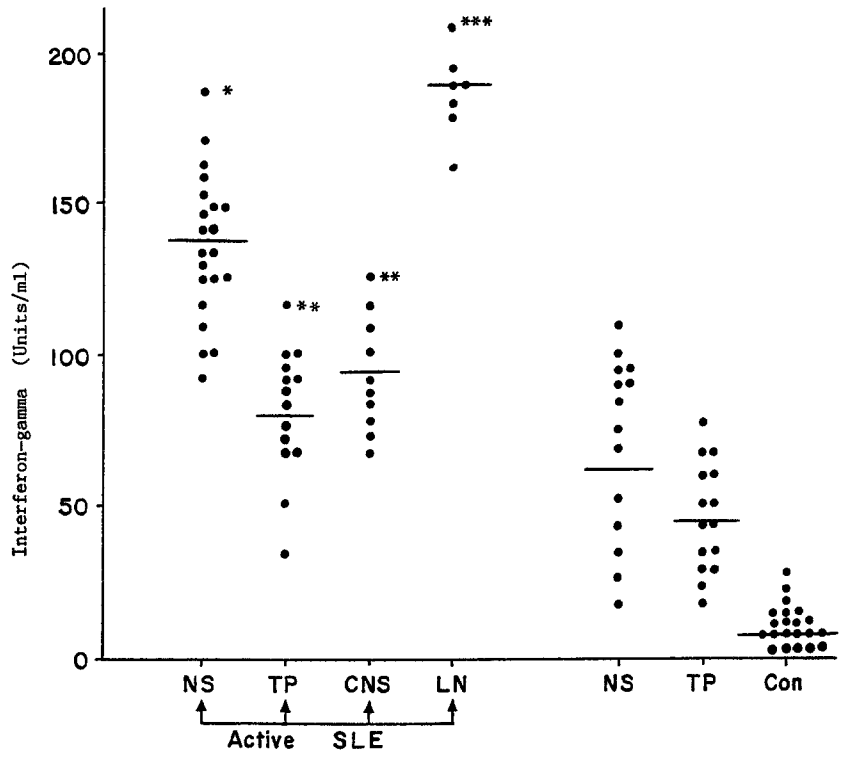

Fig. 5. Serum levels of IFN-γ in patients with active SLE associated either with NS (N = 21), TP (N = 14), CNS (N = 10) or LN (N = 7) and in patients without SLE but with NS (N = 14) or with TP (N = 15) and normal controls (Con; N = 30). (*)P <0.0001, (**)P <0.001, and (***)P <0.0001 versus normal controls.

IFN-γ remained elevated in most patients with inactive SLE, although serum levels of IL-6 declined in such patients (Figs. 1 and 2). This study also demonstrates that Con A-stimulated MNC of patients with SLE associated with LN and NS produced elevated levels of IL-6 but deficient levels of IL-2. Simultaneously such cells also produced elevated IFN-γ compared to normal controls or patients with RA. Thus a coordination exists between IL-6 and IFN-γ secretion in patients with SLE associated with NS or LN. TNFα secretion was normal from Con A-stimulated MNC of patients with SLE associated with NS or LN and patients with RA but was highly elevated in MNC of patients with SLE associated with TP.

The immune status in patients with SLE is characterized by polyclonal B-cell activation (31), a suppressor T-cell defect (32), soluble IL-2 receptor secretion (21, 33), defective IL-1 and IL-2 production (34), a T-cell defect in the delayed-type hypersensitivity reaction (13), a deficient autologous mixed lymphocytic reaction (13), abnormal representations of CD4+CD45RA+ suppressor-inducer and CD4+CD29+ helper-inducer T-cell subsets (15, 21), and elevated secretion of B-cell growth and differentiation factors (26). In spite of the extensive immunological abnormalities present in SLE, the pathogenesis and etiology of this disease are unknown. The normal human immune system eliminates invading pathogens through an inflammatory response and by the production of certain specific mediators (cytokines) that are sometimes harmful to host cells and tissues and can result in disease precipitation with substantial morbidity.

Recent evidence indicates that nearly all inflammatory processes result in the activation of monocytes, macrophages, and T cells (1–4). This activation induces many changes in the cell; among them, the most prominent is production of IL-1, IL-2, IL-6, IFN-γ or TNFα cytokines, which exert multiple effects on the host (2, 4). These effects include the induction of fever, pain, and arthralgia, the elicitation of the hepatic acute-phase response, which is accompanied by leukocytosis, and the production of acute-phase proteins (1–3). IL-2, IL-6, IFN-γ, and TNFα are the products of different genes that encode nonhomologous proteins and bind distinct receptors (4). Despite this, there is

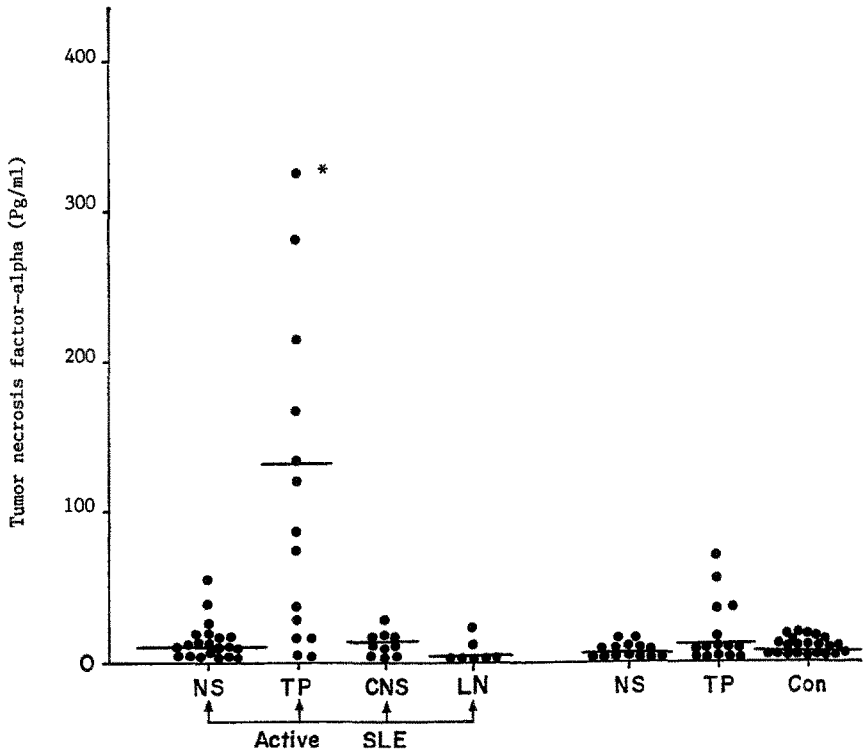

Fig. 6. Serum levels of TNFα in patients with active SLE associated with either NS (N = 21), TP (N = 14), CNS (N = 10), or LN (N = 7) and in patients without SLE but with NS (N = 14) or with TP (N = 15) and normal controls (Con; N = 30). (*)P <0.001 versus TP patients and normal controls.

considerable overlap in the cellular sources and the biological activities of these cytokines. The facts that serum IL-6 cytokine was increased in a subset of patients with SLE who have additional clinical syndromes such as LN and NS or hypogammaglobulinemia and that TNFα is increased only in patients with SLE associated with TP may indicate either that our findings are incidental to the disease

Table I. Immunologic Deficiency, IL-6, IFN-γ, and TNFα Levels in Serum of Patients with Active SLE[a]

Clinical disease and patient No.	Serum level (mg/dl)					Cytokine level		
	IgG	IgA	IgM	C3	C4	IL-6 (U/ml)	IFN-γ (U/ml)	TNFα (pg/ml)
Hypogammaglobulinemia								
1	276	34	61	64	19	86	115	90
2	251	86	43	51	8	163	92	210
3	184	53	41	27	11	69	154	170
Selective IgA deficiency								
4	1077	Tr	124	37	16	21	120	180
5	1195	0	265	54	21	36	138	260
6	1184	0	195	72	13	26	83	40
7	1308	Tr	206	48	9	24	82	110
8	1235	0	187	34	12	17	102	80
9	940	0	193	26	15	26	160	140
C4 complement deficiency								
10	2140	178	205	23	0	31	78	84
11	1110	226	173	17	0	47	106	60
12	2320	184	165	32	0	36	110	190

[a]Tr: trace, concentrations less than 5 mg/dl. Normal control values: serum IgG, 800–1250; IgA, 130–270; IgM, 150–230; C3, 68–130; and C4, 28–86 mg/dl; IL-6, 0–14 U/ml; IFN-γ, 5–28 U/ml; and TNFα, 0–37 pg/ml.

Table II. Cytokine Production by Con A-Stimulated MNC from Patients with SLE and RA[a]

Patient group	IL-2 (U/ml)	IL-6 (U/ml)	IFN-γ (U/ml)	TNFα (pg/ml)
1. SLE with NS	34 ± 11	217 ± 41*	104 ± 21*	43 ± 8
2. SLE with LN	31 ± 9	294 ± 48*	132 ± 28*	56 ± 8
3. SLE with TP	57 ± 13	102 ± 23	56 ± 16	310 ± 37*
4. RA	82 ± 16	94 ± 26	73 ± 21	38 ± 7
5. Normal controls	167 ± 34	18 ± 3	51 ± 13	31 ± 6

*$P<0.01$ compared with controls (determined by Student's t test).
[a]MNC were cultured with Con A for 48 hr and the resulting supernatants were analyzed for secretion of IL-2, IL-6, IFN-γ, and TNFα cytokines. Mean data ± SD for five patients in each group or normal controls.

pathogenesis, infection, or that changes induced by specific cytokines such as IL-6 and TNFα are important in disease manifestations and inflammatory response.

The efficacy of the human cell-mediated immune system in SLE is reflected in the wide range of clinical manifestations of the disease. The findings of elevated serum levels of IL-6 and IFN-γ in patients with SLE–NS and SLE–LN and of TNFα in SLE–TP patients suggest that they may be implicated in the pathophysiological processes of these disorders. The trigger for enhanced IL-6 and IFN-γ production in SLE and other rheumatic disease patients is unknown. Earlier, Linker-Israeli *et al.* (6) demonstrated that elevated endogenous IL-6 production is a characteristic feature of SLE. A striking increase in IL-6 levels in RA (35, 36) and PMR (37) patients was also noted. Similarly, in earlier studies (6, 38, 39) on a more extended population of SLE patients, we found a striking elevation of IL-6, IFN-γ, and TNFα levels. Our overall conclusion is that the ability of the immune system of patients with SLE and varied clinical manifestations to produce IL-2, IL-6, IFN-γ, and TNFα cytokines is not random but, instead, follows a specific pattern which is important in characterizing this disease. Our data suggest that these and probably other cytokines may have a paramount importance in the triggering and/or maintenance of multisystem disorders in SLE. Thus a immunoregulatory mechanism is likely to be involved in the system of cytokine production by lymphocytes which plays a prime role in inflammation and disease pathogenesis. It is likely that various subsets of SLE arise from the different pathogenetic processes based on the different cytokines noted.

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