Rapid report

Possible involvement of interferon alfa in the pathogenesis of fever in systemic lupus erythematosus

YOSHIHARU KANAYAMA, TOMOIKU KIM, HIROMI INARIBA, NOBUO NEGORO, MIKIO OKAMURA, TADANAO TAKEDA, AND TAKATOSHI INOUE

From the first Department of Internal Medicine, Osaka City University Medical School, 1–5–7 Asahimachi, Abeno-ku, Osaka 545, Japan

SUMMARY Serum concentrations of interferon alfa, interleukin 1, and tumour necrosis factor α were measured in 25 untreated patients with systemic lupus erythematosus (SLE). A close correlation was found between serum concentrations of interferon alfa and the degree of fever, while no significant correlations were found between fever and interleukin 1 or tumour necrosis factor α . These results suggest the possible involvement of interferon alfa in the pathogenesis of fever in SLE.

Fever is one of the cardinal symptoms of systemic lupus erythematosus (SLE). The pathogenesis of fever in patients with SLE remains unclear, however. Recent investigations showed that interleukin 1, interferon alfa, tumour necrosis factor α , and interleukin 6 are cytokines which can induce fever *in vivo*.^{1–5} We previously found an increase in the serum concentrations of interferon alfa in patients with SLE.⁶ In this study we measured serum concentrations of interferon alfa, interleukin 1, and tumour necrosis factor α in 25 untreated patients with SLE by radioimmunoassay and enzyme linked immunosorbent assay (ELISA) to examine which cytokine(s) is involved in the pathogenesis of fever in patients with SLE.

Patients and methods

Serum samples were obtained from 25 patients with SLE who fulfilled the 1982 revised criteria for the classification of SLE.⁷ None of the patients had received corticosteroids or anti-inflammatory agents at the time of serum collection. Control serum samples were obtained from 17 healthy laboratory

personnel, whose body temperatures were normal or below 36.9°C. Serum samples were stored at –80°C until assayed.

Serum concentrations of interferon alfa were measured by radioimmunoassay.⁶ The detection limit of the assay was 1 U/ml. Serum concentrations of interleukin 1 were assayed by an ELISA kit (Cistron Biotechnology, NJ, USA) using a monoclonal antibody specific for interleukin 1 β . The detection limit of the assay was 20 pg/ml. Tumour necrosis factor α concentrations were determined by a radioimmunoassay kit (Medgenix, Brussels, Belgium) using polyclonal antibody against tumour necrosis factor α . The detection limit of the assay was around 50 pg/ml.

The peak body temperature of the patient on the day of serum collection was designated as the degree of fever of the patient (body temperature was measured four times a day).

Statistics used were the Mann-Whitney U test and the non-parametric rank order correlation method where appropriate.

Results

Table 1 shows the degree of fever and serum concentrations of interferon alfa, interleukin 1 β , and tumour necrosis factor α . Serum concentrations of interferon alfa in patients with SLE were higher

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Correspondence to Dr Yoshiharu Kanayama, First Department of Internal Medicine, Osaka City University Medical School, 1–5–7 Asahimachi, Abeno-ku, Osaka 545, Japan.

than those of controls (15.4 (SD 24.0) U/ml *v* below the detection limit, $p<0.001$) and closely correlated with the degree of fever ($r_s=0.828$, $p<0.001$) (Fig. 1). Serum concentrations of interleukin 1 β were modestly increased in patients with SLE compared with controls (86.4 (SD 120.6) *v* 21.6 (47.0) pg/ml, $p<0.05$), and serum concentrations of tumour necrosis factor α were also significantly higher in patients with SLE than those in controls (256.1 (106.5) *v* 166.1 (36.6) pg/ml, $p<0.001$). Neither interleukin 1 β nor tumour necrosis factor α correlated with the degree of fever in patients with SLE ($r_s=0.097$, 0.164 respectively). Although two patients (Nos 7, 2) with the highest and the second highest interleukin 1 β concentrations were both febrile their serum concentrations of interferon alfa were also high. In contrast, patient No 17 with the third highest concentration of interleukin 1 β was not febrile and her serum concentration of interferon alfa was low. Patient No 18 with the highest serum concentration of tumour necrosis factor α was not febrile and her serum concentration of interferon alfa was low (Table 1).

Table 1 Degree of fever and serum concentrations of interferon alfa, interleukin 1 β , and tumour necrosis factor α in patients with systemic lupus erythematosus

Patient No	Degree of fever (°C)	α -INF* (U/ml)	IL-1 β * (pg/ml)	TNF- α * (pg/ml)
1	40.0	110.0	102	276
2	39.7	58.0	390	199
3	39.5	40.0	ND	286
4	39.0	23.0	ND	282
5	38.5	15.0	86	252
6	38.2	21.0	ND	395
7	38.0	23.0	480	288
8	37.9	12.0	ND	206
9	37.8	18.0	40	109
10	37.8	2.0	58	216
11	37.8	2.0	ND	197
12	37.6	5.9	38	294
13	37.4	8.1	38	168
14	37.4	2.2	ND	259
15	37.2	9.8	50	277
16	37.2	8.5	120	240
17	37.2	2.2	218	178
18	37.0	3.5	ND	679
19	37.0	2.8	65	264
20	36.8	5.2	ND	219
21	36.8	6.9	155	309
22	36.7	1.2	104	215
23	36.7	1.5	125	240
24	36.7	ND*	ND	133
25	36.7	1.2	90	222

* α -INF=interferon alfa; IL-1 β =interleukin 1 β ; TNF- α =tumour necrosis factor α ; ND=not detected, below the sensitivity limit of the assays.

Fig. 1 Correlation of the degree of fever with serum concentrations of interferon alfa (α -IFN).

Discussion

We found a close correlation between the degree of fever and the serum concentrations of interferon alfa in patients with SLE, whereas no correlations were found between the serum concentrations of interleukin 1 β or tumour necrosis factor α with fever. Patients with high serum concentrations of interleukin 1 β or tumour necrosis factor α were not febrile. Although we did not examine the temporal relation between fever and serum concentrations of these cytokines, these results suggest a possible involvement of interferon alfa in the pathogenesis of fever in SLE.

In contrast with the case of bacterial infections, febrile patients with SLE usually show leucopenia and there is no increase or only a small increase of acute phase proteins such as C reactive protein.⁸ It has been shown that interleukin 1, tumour necrosis factor α , and interleukin 6 increase the acute phase proteins,^{1 5 9 10} thus suggesting that a different cytokine may be a mediator of fever in SLE, which could explain the different febrile conditions in SLE.

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