

The relation of serum tumor necrosis factor,  
interleukin 2 receptor and gamma interferon  
levels to coronary-artery lesions in Kawasaki disease

Susumu Furukawa<sup>1</sup>, Tomoyo Matsubara<sup>1</sup>,  
Kenji Yone<sup>2</sup> and Keijiro Yabuta<sup>1</sup>

#### Abstract

We investigated 45 patients with Kawasaki disease(KD) and here report the first simultaneous determination of tumor necrosis factor (TNF), interleukin 2 receptor(IL-2R), and gamma interferon(IFN- $\gamma$ ) in the serum during acute phase. Serum levels of TNF were measured by a sandwich enzyme-linked immunosorbent assay. Serum levels of soluble IL-2R and IFN- $\gamma$  were measured by a sandwich enzyme immunoassay and radioimmunoassay, respectively. Serum levels of TNF, IL-2R, and IFN- $\gamma$  were seen to increase during the acute phase of KD. In KD patients with coronary-artery lesions(CAL), the percentage of positive cases for TNF( $\geq 10$  units/ml), IL-2R( $\geq 1056$  units/ml) and IFN- $\gamma$ ( $\geq 0.3$  units/ml) was higher than that in patients without CAL. Our results suggest that aggressive activation of immuno-competent cells develops in KD with CAL.

#### Key words

Kawasaki disease, coronary-artery lesions, TNF, IL-2R, IFN- $\gamma$

#### Introduction

We investigated whether tumor necrosis factor(TNF), interleukin 2 receptor(IL-2R), and gamma interferon(IFN- $\gamma$ ) are detectable in serum during the acute phase of Kawasaki disease(KD). TNF is a monokine secreted by activated monocytes/macrophages. IL-2 and IFN- $\gamma$  are lymphokines released by T lymphocytes in response to activation by antigens. The effect of IL-2 depends on interaction with its receptor (IL-2R) which is transiently expressed on the membrane of activated mononuclear cells and actively released in a soluble form as a result of cellular activation.

#### Materials and Methods

**Kawasaki disease:** Subjects consisted of 45 patients with acute KD who were admitted to our hospital between December 1985 and March 1989. Blood samples were taken to measure serum levels of cytokines during acute febrile stage before treatment, on the second to the ninth day. After the initiation of treatment, two-dimensional echocardiography was used to detect the presence of coronary-artery lesions(CAL). Of the 45 subjects, 11 patients showed signs of CAL during one month after onset.

---

1 Department of Pediatrics, Juntendo University School of Medicine  
2 Biotechnology Research Laboratory, Teijin Limited

*Healthy children:* Sixteen healthy children aged from five months to four years served as control subjects.

*Serum TNF, IL-2R and IFN- $\gamma$  assay:* Serum TNF levels were measured by enzyme-linked immunosorbent assay (ELISA) using monoclonal antibodies to react against human recombinant TNF (rTNF), as previously reported. Serum IL-2R levels were measured by a sandwich enzyme immunoassay using CELLFREE IL-2R test kits (T Cell Sciences, Cambridge, MA, USA). Serum IFN- $\gamma$  levels were measured by immunoradiometric assay using Human  $\gamma$ -Interferon RIA Kit (Centocor, Pa, USA).

*Statistical evaluation:* Statistical analysis was made by  $\chi^2$ -test and Student's *t* test.

### Results

Figure 1 shows the serum levels of TNF, IL-2R and IFN- $\gamma$  in KD patients during the acute phase and in control subjects. The opened circles indicate the cases with CAL. The detection limits of TNF and IFN- $\gamma$  in the serum were about 10 TNF units/ml and 0.3 IFN- $\gamma$  units/ml.

We studied how these three cytokines were related to CAL. To evaluate the three cytokine levels simultaneously in KD patients, we considered an IL-2R positive case to be one whose levels was over 1056 units/ml (mean+SD of control subjects) on serum IL-2R levels. As shown in Table 1, these cytokines were found to increase in KD patients with CAL, compared to those without CAL. The percentage of positive cases among KD patients with CAL was high for two or all of the three cytokines.

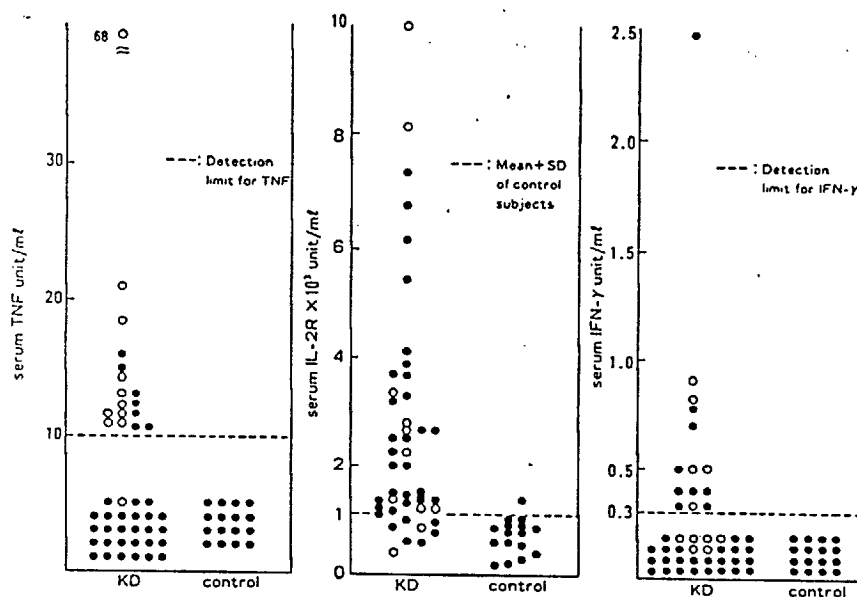


Fig.1 Serum levels of TNF, IL-2R and IFN- $\gamma$  in KD patients during the acute phase and in control subjects.

The opened circles indicate the cases with CAL.

Table 1 The percentage of positive patients for three cytokines(TNF, IL-2R and IFN- $\gamma$ ) in KD patients with and without CAL

	Positive for TNF,IL-2R and IFN- $\gamma$	Positive for two of the three cytokine	Positive for one of the three cytokines	Negative for all of the three cytokines
KD patients with CAL n=11	4/11(36.4%)	5/11(45.4%)	2/11(18.2%)	0
KD patients without CAL n=34	4/34(11.8%)	6/34(17.6%)	22/34(64.7%)	2/34(5.9%)

}  
\*  
}

KD:Kawasaki disease,CAL:coronary-artery lesion,TNF:tumor necrosis factor, IL-2R:interleukin 2 receptor,IFN- $\gamma$ :gamma interferon

\*There is a significant difference between two groups(p<0.01).

### Discussion

We have reported that serum TNF levels were found to increase during the acute phase of KD. Similarly, the increased percentages of peripheral blood monocytes/macrophages among mononuclear cells and serum TNF levels in patients with CAL were significantly higher than those found in patients without CAL. In the present study, we measured serum levels of IL-2R and IFN- $\gamma$  which are released by the activation of T lymphocytes, as well as serum levels of TNF secreted by monocytes/macrophages. In addition, we studied how these three cytokines

are related to CAL. As the results indicate, serum levels of these three cytokines were found to increase during the acute phase of KD. These cytokine levels were high in KD patients with CAL, compared to those without CAL.

In summary, several cytokines in association with activation of monocytes/macrophages and T lymphocytes, were detected in serum during acute KD. Our results suggest that aggressive activation of immunocompetent cells in KD developed in CAL.

### References

1. Furukawa, S. et al: Peripheral blood monocyte/macrophages and serum tumor necrosis factor in Kawasaki disease. Clin. Immunol. Immunopathol. 48, 247-251, 1988.
2. Yone, K. et al: Specific and sensitive sandwich enzyme immunoassay for human tumor necrosis factor- $\alpha$ . Clin. Chem. Enzym. Comms. in press.
3. Matsubara, T. et al: Serum levels of tumor necrosis factor, interleukin 2 receptor and gamma interferon in Kawasaki disease involved coronary-artery lesions. Clin. Immunol. Immunopathol. in press.



## 検索用テキスト OCR(光学的文字認識)ソフト使用

論文の一部ですが、認識率の関係で誤字が含まれる場合があります



### Abstract

We investigated 45 patients with Kawasaki disease(KD) and here report the first simultaneous determination of tumor necrosis factor(TNF), interleukin 2 receptor(IL-2R), and gamma interferon(IFN- $\gamma$ ) in the serum during acute Phase. Serum levels of TNF were measured by a sandwich enzyme-linked immunosorbent assay. Serum levels of soluble IL-2R and IFN- $\gamma$  were measured by a sandwich enzyme immunoassay and radioimmunoassay, respectively. Serum levels of TNF, IL-2R, and IFN- $\gamma$  were seen to increase during the acute phase of KD. In KD patients with coronary-artery lesions(CAL), the percentage of positive cases for TNF ( $>10$  units/ml), IL-2R ( $>1056$  units/ml) and IFN- $\gamma$  ( $>0.3$  units/ml) was higher than that in patients without CAL. Our results suggest that aggressive activation of immunocompetent cells develops in KD with CAL.