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Abstract

Cellular immunocompetence was investigated in 17 cases of aortitis syndrome (3 active, 14 inactive stage). Both the active and inactive groups demonstrated significantly lower interleukin-2 (IL-2) production than healthy volunteers. The active aortitis syndrome group produced significantly more interleukin-1 beta (IL-1 beta) than the inactive group. The proportion of CD11b+ CD8+ cells was significantly lower in the active aortitis syndrome group. Further, the proportions of CD11b- CD8+ cells and CD57+ CD16- cells in the aortitis syndrome patients were significantly higher than the healthy volunteers. These results suggest that there are intrinsic qualitative abnormalities in the T cells that produce IL-2 in aortitis syndrome. Pathogenesis of aortitis syndrome is considered as follows: during the active stage, diminished IL-2 production impairs differentiation and proliferation of suppressor T cells, thus creating abnormalities in the inhibitory functions of immunoregulation and promoting the proliferation of cytotoxic T and natural killer (NK) cells. This presumably initiates inflammation of the aorta and/or artery.

KEYWORDS: aortitis syndrome, immunocompetence, interleukin-2, interleukin-1?, lymphocyte subsets

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Cellular Immunocompetence in Aortitis Syndrome

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Cellular immunocompetence was investigated in 17 cases of aortitis syndrome (3 active, 14 inactive stage). Both the active and inactive groups demonstrated significantly lower interleukin-2 (IL-2) production than healthy volunteers. The active aortitis syndrome group produced significantly more interleukin-1β (IL-1β) than the inactive group. The proportion of $CD11b^+$ $CD8^+$ cells was significantly lower in the active aortitis syndrome group. Further, the proportions of $CD11b^-$ $CD8^+$ cells and $CD57^+$ $CD16^-$ cells in the aortitis syndrome patients were significantly higher than the healthy volunteers. These results suggest that there are intrinsic qualitative abnormalities in the T cells that produce IL-2 in aortitis syndrome. Pathogenesis of aortitis syndrome is considered as follows: during the active stage, diminished IL-2 production impairs differentiation and proliferation of suppressor T cells, thus creating abnormalities in the inhibitory functions of immunoregulation and promoting the proliferation of cytotoxic T and natural killer (NK) cells. This presumably initiates inflammation of the aorta and/or artery.

Key words : **aortitis syndrome, immunocompetence, interleukin-2, interleukin-1β, lymphocyte subsets**

Aortitis syndrome, a generic term, refers to a nonspecific chronic inflammation of unknown etiology that occurs in the aortic arch or its major branches, and may extend to the thoracic, abdominal aorta, or to the pulmonary artery in some cases. As regards the etiology, immunologic abnormalities, particularly diminished cellular immunocompetence, have been addressed (1-3). In the present study, the authors focussed on interleukin-2 (IL-2) and interleukin-1β (IL-1β), which are important for the regulation and expression of cellular immunity (4, 5), and on the lymphocyte subsets that constitute indices of cellular immunity functions. IL-2 and IL-1β production, plasma concentrations of IL-1β, and lymphocyte subsets were measured in the peripheral blood from patients with aortitis syndrome, and compared with corresponding data from healthy volunteers.

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Materials and Methods

Subjects. The present study included 17 cases of aortitis syndrome diagnosed by overall assessment of clinical symptoms, laboratory test results, angiographic and histological findings. The two men and 15 women were aged from 30 to 66 years (mean 46.7 years). Those patients presenting with a 1-h erythrocyte sedimentation rate (ESR) of more than 40 mm associated with a persistent positive reaction for C-reactive protein (CRP) were classified in the active group. Patients with a 1-h ESR less than 40 mm and a negative CRP reaction were classified in the inactive group. One out of the 3 cases in the active group, and 6 of the 14 cases in the inactive group were receiving steroid medication.

Sixteen healthy volunteers were included as controls. All of the them were women, aged from 32 to 66 years (mean 48.4 years).

Measurement of IL-2 production. Lymphocytes were separated from heparinized peripheral blood by density gradient centrifugation, and resuspended in culture medium (RPMI-1640 containing 5 % fetal bovine serum (FBS)) to achieve a lymphocyte count of 2×10^6 cells/ml. Then, 0.5 ml of the lymphocyte suspension plus 0.5 ml of concanavalin A (ConA) were dispensed to each

well of a 24-well multiplate, thereby adjusting the lymphocyte count to 10^6 cells/well and the ConA concentration to 5.0 μg/ml. The plates were incubated at 37°C in a 5 carbon dioxide atmosphere for 21 h. Then, the supernatant was collected and the IL-2 concentration measured by a radioimmunoassay of two-antibodies method using an Amersham Interleukin-2 [I^{125}] Assay Kit.

Measurement of IL-1β production. Mononuclear cells (MNC) were separated from heparinized peripheral blood by density gradient centrifugation, and resuspended in culture medium (RPMI-1640 containing 10 % FBS) to achieve an MNC count of 1×10^6 cells/ml. Aliquots of 0.5ml of the MNC suspension plus 0.5 ml of lipopolysaccharide (LPS) were dispensed to each well of a 24-well multiplate, and the LPS concentration adjusted to 10 μg/ml. The plates were incubated at 37°C in a 5 carbon dioxide atmosphere for 24 h. Then, the supernatant was collected and the IL-1β concentration measured by ELISA using a Cistron IL-1β ELISA Kit. The detection limit of this kit is 0.5 ng/ml.

Assay of plasma IL-1β concentration. Plasma was obtained from peripheral blood samples by centrifugation, and the IL-1β concentration was directly measured by ELISA.

Determination of lymphocyte subsets. Fluorescein isothiocyanate (FITC) labelled monoclonal antibody and phycoerythrin (PE) labelled monoclonal antibody 50 μl each were added to 100 μl of the heparinized peripheral blood samples, and the mixture was incubated at 4°C for 30 min. After reaction, 3 ml of an erythrocytolytic agent was added, and the mixture was standstill for 15 min at room temperature. Phosphate buffered saline (PBS) was added, and the preparation was washed by centrifugation at 1,000 rpm and 4°C for 10 min. One ml PBS was added to resuspend the pellet, and the lymphocytes subsets were counted with a flow cytometer (FCM-1D, Nippon Bunko).

The monoclonal antibodies used in the measurements comprised FITC labelled Leu7 (CD57) and Leu4 (CD3) antibodies, PE labelled Leu2a (CD8), Leu11c (CD16) and HLA-DR antibodies (Becton & Dickinson), FITC labelled T4 (CD4), Mol (CD11b) and PE labelled 2H4 (CD45RA) antibodies (Coulter), and FITC labelled NUT2 (CD25) antibody (Nichirei). The antibody combinations employed in two-color analysis were CD4 plus CD45RA, CD11b plus CD8, CD57 puls CD16, CD3 plus HLA-DR, CD4 plus HLA-DR, and CD8 plus HLA-DR. CD25 antibodies were employed for single-color analysis.

Statistical analysis. The results were expressed as mean ± standard deviation, and differences between the two groups were assessed by Student's *t*-test. Difference was considered statistically significant when the P value was level less than 5 percent.

Results

The IL-2 production of the aortitis syndrome patients (192.1 ± 100.8 pg/ml) was significantly lower ($p < 0.01$) than the controls' (390.5 ± 144.9 pg/ml) (Fig. 1). Regarding, active *versus* inactive status, the IL-2 production of both active (191.7 ± 86.2 pg/ml) and inactive (192.2 ± 106.6 pg/ml) groups was significantly lower ($p < 0.05$ and $p < 0.01$, respectively) than the controls' (Fig. 2). The

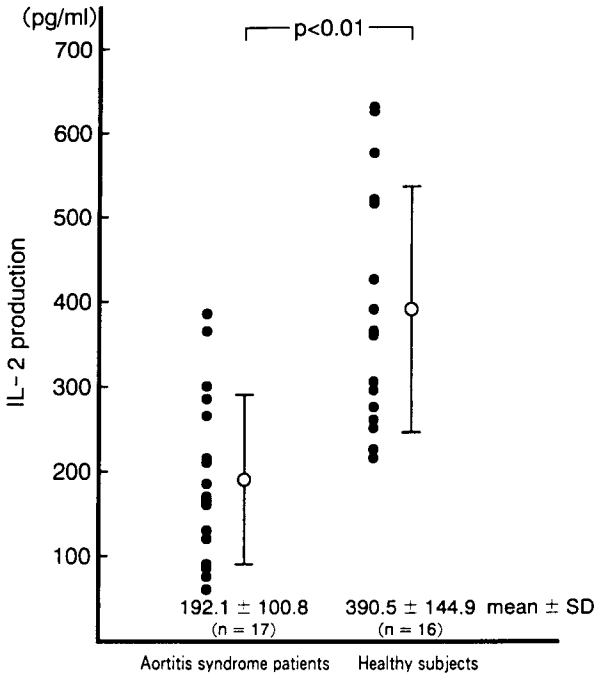

Fig. 1 IL-2 production in aortitis syndrome patients and healthy subjects.

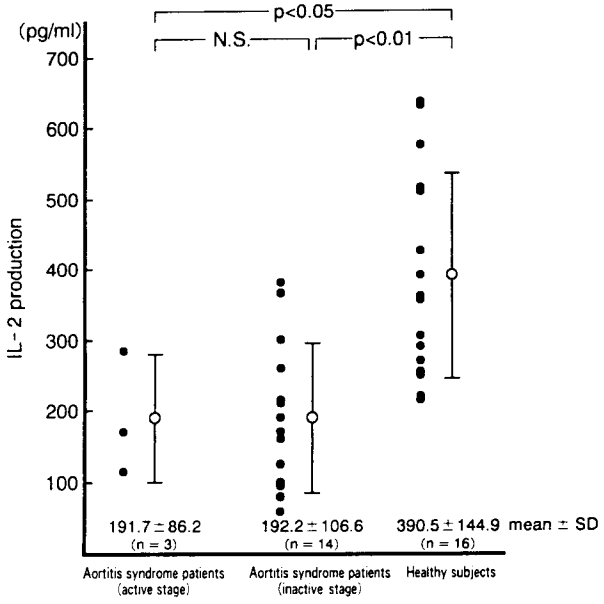

Fig. 2 IL-2 production in active and inactive stages of aortitis syndrome.

IL-2 production for both steroid users 138.4 ± 73.0 pg/ml and non-users 229.7 ± 103.4 pg/ml was significantly lower ($p < 0.01$) than the controls'.

IL-1β production among the aortitis syndrome patients (12.0 ± 8.7 ng/ml) tended to be higher than the corresponding level among the healthy subjects (10.3 ± 4.1 ng/ml), but this difference was not statistically significant (Fig. 3). However, the IL-1β production in the active group (23.7 ± 10.4 ng/ml) was significantly higher ($p < 0.01$) than the inactive group (9.5 ± 6.2 ng/ml) (Fig. 4). Neither the active nor the inactive group showed a significant difference related to the healthy group. Further, the IL-1β production in both the steroid-treated group (12.1 ± 9.5 ng/ml) and the non-steroid group (11.9 ± 8.7 ng/ml) was not significantly different from that of the healthy subjects. No significant difference between the steroid and non-steroid groups was observed.

Plasma IL-1β level was below the detection sensitivity of the kit in all 33 cases assessed in this series.

The proportion of $CD4^+$ $CD45RA^+$ cells was 13.4 ± 4.5 % among the aortitis syndrome patients and 14.0 ± 6.8 % among the healthy subjects, but this difference was not statistically significant. Also, the proportions in both the active group (13.7 ± 6.6 %) and the inactive group (13.4 ± 4.3 %) were not significantly different from that of the healthy group. The proportion of $CD4^+$ $CD45RA^-$ cells was 30.5 ± 6.0 % for the aortitis syndrome patients and 31.4 ± 6.0 % for the healthy subjects, showing no significant difference. The proportion was higher for the active group (34.3 ± 3.5 %) than for the inactive group (29.7 ± 6.2 %), but neither group differed significantly from the healthy group.

The proportion of $CD11b^+$ $CD8^+$ cells for the aortitis syndrome patients (6.3 ± 4.6 %) did not differ significantly from the healthy subjects' (6.1 ± 2.8 %). However, the proportion in the active group (2.3 ± 1.5 %) was significantly lower ($p < 0.05$) than the healthy subjects (Fig. 5). $CD11b^-$ $CD8^+$ cell proportions demonstrated no significant difference between the active aortitis syndrome group (24.8 ± 7.8 %) and the inactive group (23.1 ± 7.5 %). However, the proportion for the overall aortitis syndrome patients (23.4 ± 7.3 %) was significantly higher ($p < 0.05$) than the healthy subjects' (19.0 ± 4.4 %) (Fig. 6).

The proportion of $CD57^+$ $CD16^+$ cells was 8.9 ± 5.6 % for the aortitis syndrome patients and 11.5 ± 5.9 % for the healthy subjects. Moreover, neither the correspond-

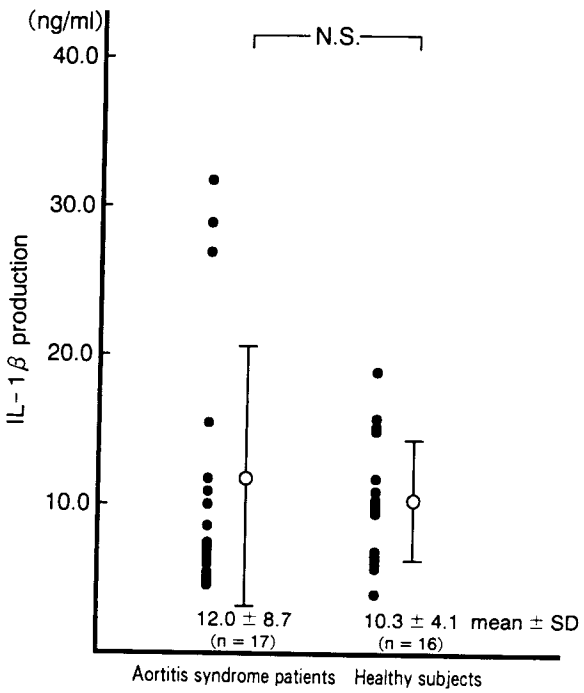

Fig. 3 IL-1β production in aortitis syndrome patients and healthy subjects.

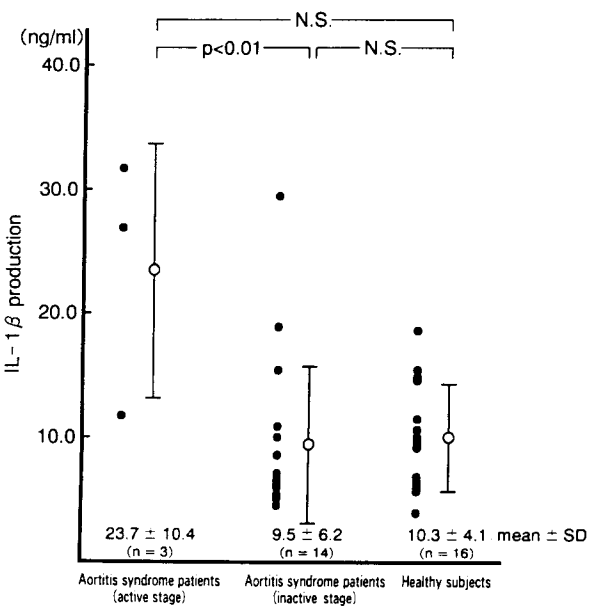

Fig. 4 IL-1β production in active and inactive stages of aortitis syndrome.

ing values for the active group (7.3 ± 2.7 %) nor those for the inactive group (9.2 ± 6.1 %) had significant differences from those of controls. The proportion of $CD57^+$ $CD16^-$ cells was significantly increased ($p < 0.05$) among the aortitis syndrome patients (13.4 ± 6.9 %) as compared with the healthy subjects (8.8 ± 4.0 %) (Fig. 7). However, there was no significant difference in this aspect between the active group (10.6 ± 3.7 %) and the inactive group (13.9 ± 7.4 %). Regarding the proportion of $CD57^-$ $CD16^+$ cells, the values for the aortitis syndrome patients (4.4 ± 1.8 %) and the healthy subjects (4.7 ± 1.5 %) were not significantly different, but those for the active group (2.1 ± 0.5 %) were significantly lower ($p < 0.05$) than the inactive group' (4.8 ± 1.6 %).

The proportions of $CD3^+$ HLA-DR^+ cells among the aortitis syndrome patients (6.2 ± 2.7 %) and the healthy subjects (6.2 ± 3.6 %) were not significantly different, also the corresponding proportions in the active group (4.7 ± 3.0 %) and the inactive group (6.5 ± 2.7 %) were not significantly different from those of the healthy subjects. Likewise, the proportion of $CD4^+$ HLA-DR^+ cells in the aortitis syndrome patients (2.1 ± 0.9 %) was not

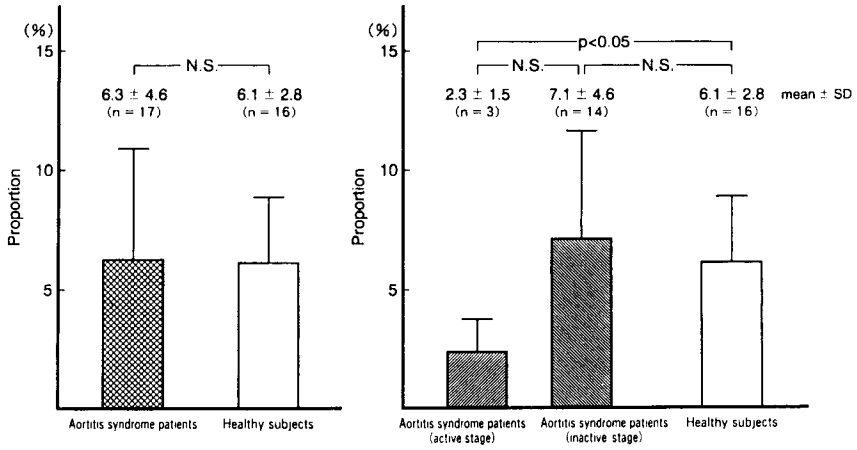

Fig. 5 Proportion of $CD11b^-$ $CD8^+$ cells in active and inactive stages of aortitis syndrome and in healthy subjects.

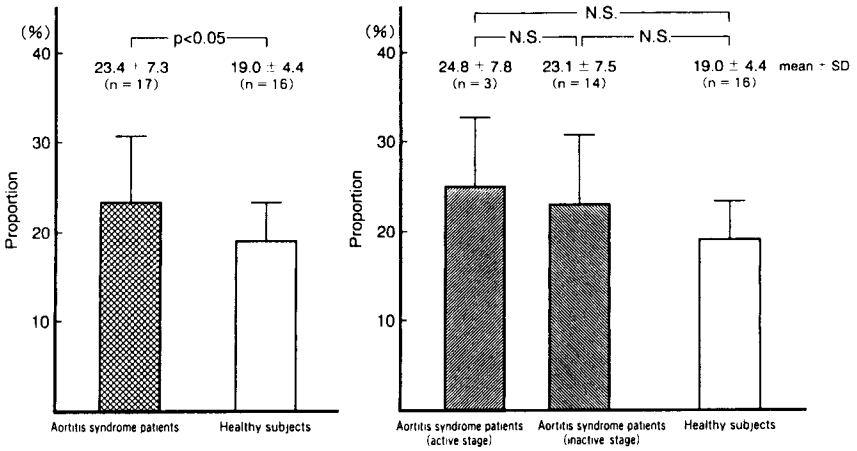

Fig. 6 Proportion of $CD11b^-$ $CD8^+$ cells in active and inactive stages of aortitis syndrome and in healthy subjects.

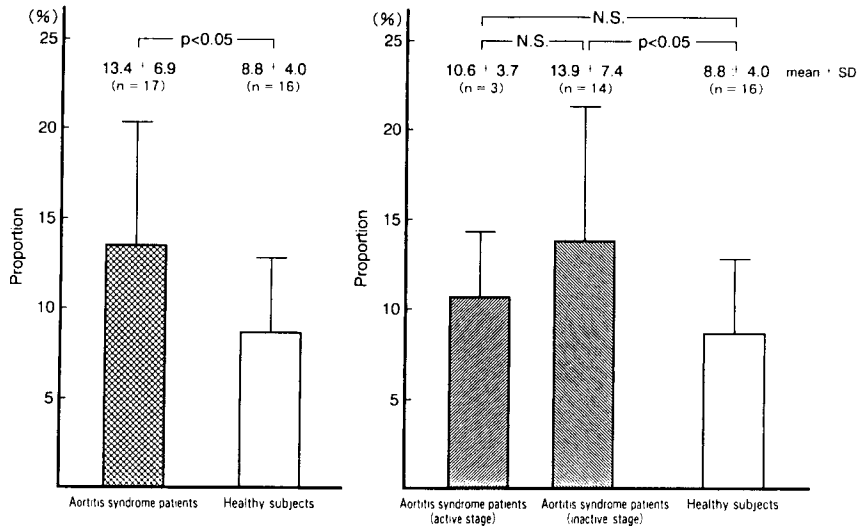

Fig. 7 Proportion of $CD57^+$ $CD16^-$ cells in active and inactive stages of aortitis syndrome and in healthy subjects.

significantly different from that in the healthy subjects (2.5 ± 1.2 %), and neither the proportion for the active group (2.0 ± 1.3 %) nor that for the inactive group (2.2 ± 0.9 %) showed a statistically significant difference from that for the healthy subjects. The proportion of $CD8^+$ $HLA\text{-}DR^+$ cells observed in the aortitis syndrome patients (3.8 ± 2.0 %) showed no significant difference from the healthy subjects' (3.8 ± 2.8 %). However, the proportions in the active group (2.6 ± 1.9 %) tended to be lower than those in the inactive group (4.0 ± 2.0 %). Finally, the proportions of $CD25^+$ cells among the aortitis syndrome patients (1.8 ± 0.9 %) and those among the healthy subjects (1.9 ± 1.4 %) were not significantly different, and there was no significant difference between the proportions in the active group (1.7 ± 1.0 %) and the inactive group (1.9 ± 0.9 %).

Discussion

The aortitis syndrome is characterized by obstructive lesions due to nonspecific chronic inflammation at the aorta or at its major branching sites, and the etiology of this syndrome still remains obscure. More recently, attention has been paid in relation to the etiology of this syndrome. Among the causes, infection including tuberculosis, genetic factors, and hormonal abnormalities (6) have been pointed out. Since Judge *et al.* (7) asserted that autoimmunity is involved in the pathogenesis of this syndrome, many reports have appeared in this connection, supporting the idea of immunological mechanisms to play a role in this disorder. Particularly, studies on cellular immunity have revealed that patients in the active stage of the aortitis syndrome present characteristics of decreased response in delayed skin reactions, such as the tuberculin reaction and the dinitrochlorobenzene (DNCB) skin reaction (1), as well as decreased reactivity of peripheral blood lymphocytes with respect to the phytohemagglutinin (PHA) induced blast transformation (2). Many other forms of depressed cellular immunocompetence; decreased proportions of T cells among the peripheral blood lymphocytes and decreased PHA-induced lymphoblast transformation rates, reportedly occur in aortitis syndrome patients in the active and inactive stages (3).

IL-2 manifests important actions; promoting proliferation of T cells, activating cytotoxic T cells, inducing differentiation of B cells, activating NK cells, inducing lymphokine-activated killer (LAK) cells and inducing formation of IL-2 receptors, and thereby plays a key role in cellular immunoregulation (4). Alcocer-Varela *et al.* (8) have reported that, compared to healthy individuals, the IL-2 production of aortitis syndrome patients in both the active and inactive stages is depressed, and in particular is significantly depressed in the active stage. In the present

study also, although no significant differences between the active and inactive groups were observed, both groups had significantly lower IL-2 production than the healthy subjects.

HLA-DR$^+$ cells are regarded as activated T cells (9). The results of the present study revealed that the proportions of CD3$^+$ HLA-DR$^+$ cells, CD4$^+$ HLA-DR$^+$ cells, and CD8$^+$ HLA-DR$^+$ cells in both active and inactive stages of aortitis syndrome were not significantly different from the corresponding proportions in healthy subjects, indicating that the proportion of activated T cells is not particularly elevated even in active stages. Hence, the conjecture that *in vitro* decreases in IL-2 production are due to prior *in vivo* activation and consequent exhaustion of the IL-2 production of the T cells before *in vitro* cultivation appears implausible.

CD4$^+$ cells are divided into the two subsets of helper and suppressor-inducer T cells on the basis of reactivity with CD45RA antibody (10). Of these two categories, the helper T cells are considered to be primarily responsible for IL-2 production (10). Alcocer-Varela *et al.* showed that both the proportion and absolute number of CD4$^+$ cells were lower in aortitis syndrome patients than in the controls (8). However, they did not subclassify CD4$^+$ cells into helper or suppressor-inducer T cells. Our results for CD4$^+$ CD45RA$^-$ cell proportion (helper T cells) was not significantly different, in either the active or inactive aortitis syndrome group, from the healthy subjects'. Hence, an explanation attributing the results to a decrease in the number of IL-2-producing helper T cells also appears implausible.

The subset of CD8$^+$ cells can be subdivided into CD11b$^+$ CD8$^+$ cells, regarded as being suppressor T cells, and CD11b$^-$ CD8$^+$ cells, regarded as being cytotoxic T cells (11). However, in the present study, the proportion of CD11b$^+$ CD8$^+$ cells, (*i.e.*, putative suppressor T cells) among all the aortitis syndrome patients was not significantly different from the healthy subjects'. Because the proportion of suppressor T cells in the active group was actually lower, the conjecture that IL-2 production diminished through inhibition by suppressor T cells also seems improbable. Further, CD25$^+$ cells are regarded as low-affinity IL-2 receptors (12), but in our study, there was no significant difference in the proportion of CD25$^+$ cells among the active, inactive, and healthy group'. This may exclude the conjecture attributing decreased IL-2 production to diminished expression of low-affinity IL-2 receptors. Production of IL-2 by T-lymphocytes requires IL-1 production by antigen-presenting cells, mainly macrophages (13), but results of this study indicated that IL-1β production was well maintained in both the active and inactive aortitis syndrome groups, which seems to exclude the hypothesis of functional abnormalities in macrophages. Indeed, the fact that diminished IL-2 production was recognized in the active stage and in the inactive stage of aortitis syndrome, even years after the onset of the disease, indicates that, as reported with reference to patients with systemic lupus erythematosus (SLE) (14, 15) and other immunodeficiencies (16), decreased IL-2 production is actually due to qualitative abnormalities. This suggests the possibility of intrinsic defects of T cells in aortitis syndrome. Thus, one may infer that abnormalities in IL-2 production may be the phenomenon involved in the pathogenesis of aortitis syndrome.

IL-1 has α and β forms, with different isoelectric points, but these two forms are thought to bind to the same receptors and to exhibit similar biological activity (17). IL-1 plays an important role in the acute-phase of the inflammatory response and in immunoregulatory functions; including endogenous pyrogenic activity, synthesis of acute inflammatory proteins such as haptoglobin (18), action upon vascular endothelial cells and fibroblasts to promote proliferation of capillaries and fibroblasts (19). The mononuclear cells in the peripheral blood of patients with Kawasaki's disease, characterized by inflammatory angiitis and similar to the aortitis syndrome, also show increased IL-1β production (20). The circulating level of IL-1β is significantly elevated in patients with Kawasaki's disease (21). IL-1 involvement in another inflammatory disorder has been reported, *e.g.*, strong IL-1 activity has been demonstrated in the synovial fluid and the supernatants of synovial membrane cell cultures obtained from patients with rheumatoid arthritis (22). Our results that IL-1β production in patients with active aortitis syndrome was significantly increased indicate that IL-1 may be somehow involved in the onset and further development of aortic inflammation. In particular, the local production of IL-1β infiltrated macrophages in the severely inflamed aortic media and adventitia may play an important role in the onset, progression, and continuation of aortic wall inflammation. Plasma concentrations of IL-1β were under the limit of detection of the kit in the all patients with aortitis syndrome in the present study. However, this does not exclude the possibility of IL-1β involvement on the pathogenesis of the aortitis syndrome. Since

IL-1β is locally produced, its concentrations in peripheral blood were extremely low, and below the detection sensitivity.

Pronounced infiltration of $CD8^+$ lymphocytes and cytotoxic T cells into the arterial wall of specimens excised from aortitis syndrome patients has been reported in immunohistological studies (23-25). Similarly, our results showed that the proportion of $CD11b^-$ $CD8^+$ cells (11) in the peripheral blood of aortitis syndrome patients was significantly elevated, indicating that cytotoxic T cells play a major role in the onset and progression of aortic inflammation.

NK cells, possessing cytotoxic activity, can be divided into three subtypes according to their reactivity with CD57 and CD16 antibodies; $CD57^-$ $CD16^+$ cells (strong activity) $CD57^+$ $CD16^+$ cells (intermediate activity), and $CD57^+$ $CD16^-$ cells (weak activity) (26). In the aortitis syndrome, the proportions of the cells with strong or intermediate activity, were the same as the controls', but the proportions of $CD57^+$ $CD16^-$ cells were significantly elevated. Furthermore, this proportion was higher in the inactive stage than the active stage. These findings may indicate that NK cells, rather than being involved in the development of cytotoxic expression during the acute inflammatory stage, are more closely related to the maintenance of inflammatory phenomena during the inactive stage of aortitis syndrome.

Further, the fact that the proportions of $CD11b^+$ $CD8^+$ cells, considered to be suppressor T cells (11), were significantly lower in the active aortitis syndrome group than the healthy subjects indicates the possibility that the decrease in IL-2 production impaired differentiation into and proliferation of suppressor T cells. This could create abnormalities in the inhibitory functions of immunoregulation, promote proliferation of cytotoxic T cells, and cause aortic and/or arterial inflammation through the mediation of IL-1β.

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