Serum Levels of Interleukin 15 in Patients with Rheumatic Diseases

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ABSTRACT. ***Objective***. The role of the cytokine interleukin 15 (IL-15) in rheumatic disease is unclear. We examined serum levels of IL-15 in patients with various rheumatic diseases.

Methods. Serum levels of IL-15 were determined by sandwich ELISA.

Results. Serum levels of IL-15 were significantly increased in patients with polymyositis/dermatomyositis, polyarteritis nodosa, and systemic sclerosis; and significantly increased as well in disease complicated by interstitial pneumonitis (IP), hemophagocytic syndrome (HPS), and/or vasculitis. Patients with serum IL-15 levels ≤ 5 pg/ml showed significantly high rates of survival.

Conclusion. IL-15 is related to the pathogenesis of IP, HPS, and/or vasculitis. Serum IL-15 level could possibly be used as a marker of prognosis. (J Rheumatol 2001;28:2389–91)

Key Indexing Terms:
INTERLEUKIN 15
DERMATOMYOSITIS/POLYMYOSITIS
INTERSTITIAL PNEUMONITIS
POLYARTERITIS NODOSA
SYSTEMIC SCLEROSIS
HEMOPHAGOCYTIC SYNDROME

Interleukin 15 (IL-15) is a pleiotropic cytokine, derived from several cell types including macrophages and fibroblasts[1], which mediates its activity through a heterotrimeric receptor consisting of a unique IL-15Rα chain, in combination with the ß and γ chains of the IL-2 receptor[2]. IL-15 can induce T cell proliferation[1], B cell maturation and isotype switching[3], and natural killer cell cytotoxicity and cytokine generation[4], and may protect T cells from apoptosis[5]. The role of IL-15 in the context of any pathological situation remains to be elucidated; the role of IL-15 in rheumatic disease is currently unclear.

We investigated the serum level of IL-15 in patients with various rheumatic diseases by sandwich enzyme linked immunosorbent assay (ELISA) and correlated the results to disease prognosis.

MATERIALS AND METHODS

Patients. Patients with various rheumatic diseases were enrolled for study (Table 1). Seventy-nine were women and 16 men, and their ages ranged from 16 to 74 years (mean 42). Some patients had concomitant complications such as interstitial pneumonitis (IP), vascular lesion, and/or hemophagocytic syndrome (HPS). All patients were diagnosed by respective criteria for the specific disease[6-9].

Serum levels of IL-15. Serum levels of IL-15 were determined with the Quantikine Human IL-15 ELISA kit (R&D Systems, Minneapolis, MN, USA). The range of the standard curve was between 0.1 and 250 pg/ml, and this assay is capable of detecting IL-15 concentrations > 0.1 pg/ml.

Statistical analysis. The StatView program (Version J4.0.2, Abacus Concepts, Inc.) was utilized to analyze results. Student's t test was applied to analyze the difference in the levels of IL-15 in serum between patients and healthy controls. Chi-squared test was applied to analyze the relation between serum levels of IL-15 and patient prognosis.

RESULTS

Serum levels of IL-15 in patients with polyarteritis nodosa (PAN) including antineutrophil cytoplasmic antibody (ANCA) associated vasculitis, polymyositis/dermatomyositis (PM/DM), and systemic sclerosis (SSc) were significantly higher than in controls ($p < 0.005$, $p < 0.05$, $p < 0.05$, respectively). Although some patients with rheumatoid arthritis or systemic lupus erythmatosus (SLE) tended to have higher levels of serum IL-15, these findings were not of significance (Figure 1A). Patients with IP had significantly higher levels of IL-15 than controls ($p < 0.05$), although there was no difference between patients with or without IP. One patient with intestinal vasculitis and PM/DM had a high level of IL-15. Patients with HPS had significantly higher levels of IL-15 than controls ($p < 0.05$). Thus, higher levels of IL-15 were related to IP, vasculitis, and HPS (Figure 1B).

Next we examined the relation between serum IL-15 levels and prognosis. Patients with serum IL-15 levels < 5 pg/ml revealed significantly higher survival rates compared to those with > 5 pg/ml, as shown in Table 2. Thus, serum level of IL-15 is related to prognosis of the disease.

DISCUSSION

Studies have shown that cytokine abnormalities contribute to the pathogenesis of rheumatic diseases[10,11]. We examined

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Table 1. Patient profiles in various rheumatic diseases (total n = 95).

Disease	Complications		
	with IP, n = 20	Vasculitis, n = 11	HPS, n = 6
RA (n = 11)	2	0	0
SLE (n = 53)	3	0	6
PM/DM (n = 11)	7	1	0
PAN* (n = 10)	4	10	0
SSc (n = 7)	3	0	0
MCTD (n = 3)	1	0	0

* Including antineutrophil cytoplasmic antibody related vasculitis. PAN: polyarteritis nodosa, SSc: systemic sclerosis, MCTD: mixed connective tissue disease, IP: interstitial pneumonitis, HPS: hemophagocytic syndrome.

Table 2. Serum IL-15 level and survival rate.

	IL-15	
	> 5 pg/ml	< 5 pg/ml
Survival rate, %	55 (11/20)	95.8* (91/95)

* $p < 0.001$. Significant differences between IL-15 > 5 pg/ml and < 5 pg/ml determined by chi-square test.

serum levels of IL-15 in patients with various rheumatic diseases. Serum IL-15 levels were increased in SSc, PM/DM, and PAN. We expected an increase in patients with SLE, since other studies have reported on the increase of IL-2[10], which shares a common receptor with IL-15. However, most patients with SLE did not show an increase of IL-15. This result suggests that IL-15 is involved in a different role compared to IL-2 and other cytokines such as IL-6 or IL-10 in SLE[11].

The increased levels of serum IL-15 in SSc, PM/DM, and PAN are related to specific clinical manifestations (IP, vasculitis). Because the lung and skeletal muscle produce more IL-15 than other tissues[1], hyperproduction of IL-15 from these tissues may induce activation of T cells in patients with PM or IP. Moreover, endothelial cells produce IL-15[12]; thus increased serum levels of IL-15 in vasculitis may be correlated to its hyperproduction from the endothelium. IL-15 also itself has the potential to induce a vascular permeability factor from peripheral blood mononuclear cells[13]: it is possible IL-15 production by local tissues may lead to deterioration of the condition of the disease. Although other factors such as renal clearance or metabolism of receptor binding pharmacokinetics should be considered[14], it is suggested that the serum level of IL-15 depends on the local level of IL-15 production.

The most interesting finding was that significantly increased levels of serum IL-15 seemed to correlate with poor survival rates. This may be a coincidence, but it is worth further investigation. Indeed, the serum levels of IL-15 in patients with improvement decreased, while in the deceased patients the serum level of IL-15 did not decrease. Thus, this relation to prognosis suggests that IL-15 plays an important role in rheumatic disease, and can be utilized as a prognostic measure of disease.

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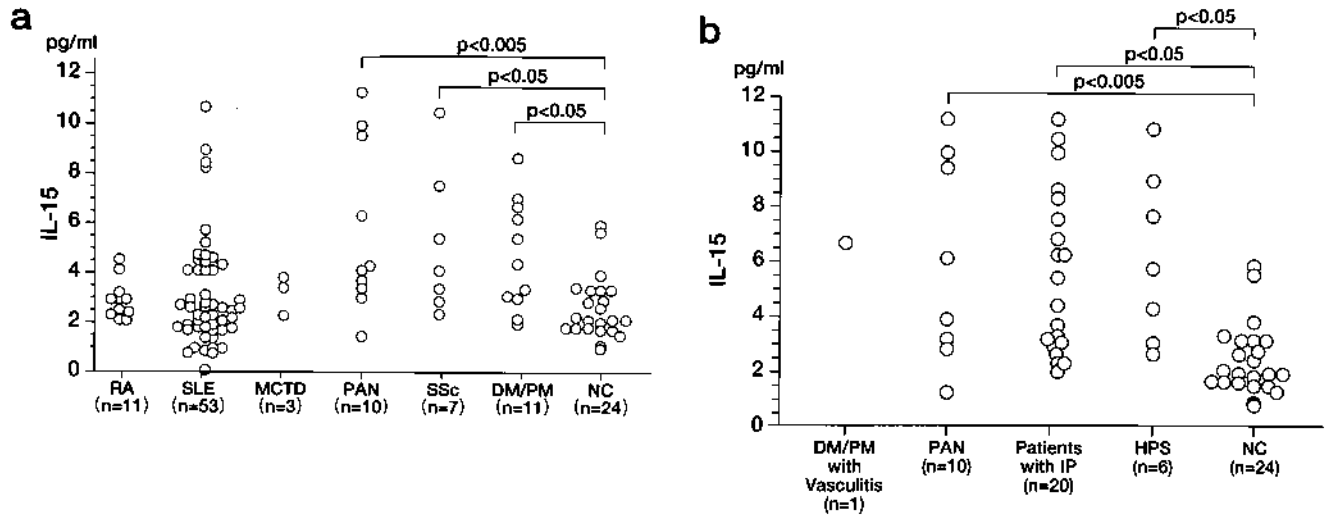

Figure 1. a. Serum IL-15 levels in patients with various rheumatic diseases. Serum samples from patients with PAN, SSc, and PM/DM had significantly higher IL-15 levels than controls: $p < 0.005$, $p < 0.05$, $p < 0.05$, respectively. b. Serum IL-15 levels in rheumatic disease with complications. Patients with PAN, rheumatic disease with IP, and HPS had significantly higher IL-15 levels than controls: $p < 0.005$, $p < 0.05$, $p < 0.05$, respectively. RA: rheumatoid arthritis, SLE: systemic lupus erythematosus, MCTD: mixed connective tissue disease, PAN: polyarteritis nodosa, SSc: systemic sclerosis, DM/PM: dermatomyositis/polymyositis, IP: interstitial pneumonitis, HPS: hemophagocytic syndrome, NC: normal control.

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