Increased serum IgE level and interleukin-4 release from cultured lymphocytes from a patient with adult onset Still's disease

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Abstract

Objective—To evaluate the relationship between high serum levels of IgE and the release of interleukin-4 (IL-4) from cultured lymphocytes of a patient with adult onset Still's disease.

Methods—IL-4 concentrations in plasma and culture from inactivated peripheral blood mononuclear cells were assessed by enzyme immunoassay during febrile episodes and remission.

Results—A high level of IL-4 was detected by enzyme immunoassay in the peripheral blood mononuclear cells cultured from the patient. These seemed to correspond with a febrile episode and a high serum IgE concentration.

Conclusion—Increased serum IgE concentrations during a febrile episode are rare in patients with adult onset Still's disease, but the relationship between the high levels of serum IgE and IL-4 in cultured lymphocytes may provide clues to pathogenesis of the condition.

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Adult onset Still's disease (AOSD) is a chronic multisystemic inflammatory disorder of unknown origin that is characterised by high spiking fever, polyarthralgia, a salmon pink evanescent rash, lymphadenopathy, and hepatosplenomegaly.¹ Features of the disease usually include an increased erythrocyte sedimentation rate (ESR), leucocytosis, liver dysfunction, negativity for rheumatoid factor (RF) and antinuclear antibodies (ANA), and a notably increased incidence of hyperferritinemia. In general, however, this disease lacks specific clinical, laboratory, and histological features.²⁻⁴ We describe a 19 year old Japanese woman with AOSD who showed markedly increased concentrations of both serum IgE and interleukin-4 (IL-4) in lymphocytes cultured during febrile episodes.

Case report

A 19 year old Japanese woman presented in September 1991 with a sore throat, joint pain, intermittent rash on the trunk and proximal limbs, and fever of one month duration. She had had no similar attacks previously. The illness did not respond to administration of piperacillin, and she was admitted to our hospital. There was no history of allergy or

relevant family history. Physical examination revealed a salmon coloured rash on the trunk, arms, and thighs with typical Kbner's phenomenon, diffuse redness of the pharynx with no exudation, and hepatosplenomegaly. She also had cervical lymphadenopathy which was slightly tender and movable, and arthralgia of both wrists, with limited movement. Laboratory data on admission showed peripheral blood counts as follows: haemoglobin 136 g/l; total leucocyte count 6300/mm³ with 56% neutrophils; ESR 52 mm/1st h; normal platelet count. Lactic dehydrogenase (LDH) was increased to 706 IU/l (normal value (NV) < 420 IU/l) and serum ferritin of 358 ng/ml (< 80 ng/ml). No circulating immune complexes were detected. Serological tests for viral infection were negative. The serum polyclonal IgE concentration was markedly increased, to 2360 U/ml (NV < 400 U/ml), though serum concentrations of IgG, IgA, and IgM were normal. There were no detectable levels of specific IgE antibodies examined by radio-immunosorbent tests against a standard series of food, animal, pollen, and fungal antigens. The electrocardiogram and chest radiograph were normal. An abdominal computed tomograph scan showed hepatosplenomegaly and multiple small para-aortic lymphadenopathy. Findings met the criteria for diagnosis of AOSD.

The patient was treated with non-steroidal anti-inflammatory drugs (NSAIDs), and her symptoms improved within two weeks, when the cervical lymphadenopathy and hepatosplenomegaly were no longer apparent and inflammation decreased, as reflected by an ESR of 12 mm/1st h. The increased concentrations of LDH and ferritin decreased one week after NSAID treatment was started. Serum IgE also decreased, to 450 U/ml (NV < 400 U/ml). However, eight months later, in May 1992, the fever, wrist pain, and rash recurred. Laboratory data again revealed an accelerated ESR of 36 mm/1st h, but serum LDH and ferritin concentrations were normal. Serum IgE was again markedly increased, to 3480 U/ml (NV < 400 U/ml). A bone marrow aspirate and cervical lymph node biopsy specimen showed reactive hyperplasia, but no other characteristic findings. NSAIDs were administered again and the patient's symptoms subsided after one week. The serum IgE level became normal (440 U/ml) three months after the second attack.

We investigated a possible association of increased plasma IL-4 with the increased IgE

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Concentrations of serum IgE and interleukin-4 (IL-4) in cultures of lymphocytes from a patient with adult onset Still's disease during febrile episodes and periods of remission

Episodes	IgE (U/ml)	IL-4 (pg/ml)
First attack	2360	NM
First remission	450	< 50
Second attack	3480	1120
Second remission	440	< 50
NV	< 400	< 50

NM = not measured; NV = normal value.

concentrations. Plasma IL-4 was measured by immunoenzymetric assay using Inter Test 4 (Genzym, USA).⁵ It was undetectable in plasma samples that had been frozen immediately after collection, even when the serum IgE levels were extremely high (data not shown). Peripheral blood mononuclear cells (PBMCs) were isolated from the patient's heparinised blood using Ficoll/Hypaque centrifugation, and cultured in HY 640 medium for two days at 37°C and 5% carbon dioxide without stimulation.⁵⁻⁶ The supernatants were harvested and analysed for IL-4. The IL-4 concentration was found to be increased in samples from the second febrile episode, but not during the two periods of remission (table). Measurements were not made in relation to the first attack.

Discussion

We have described a patient with AOSD who showed markedly increased serum concentrations of IgE during two febrile episodes. Increased concentrations of some immunoglobulins (especially IgG and IgM) are common in such episodes, but increases in IgE and IgA occur infrequently.^{2-3,7} Studies of Japanese patients with a definite diagnosis of AOSD who had increased IgE revealed the concentrations to be in the range 2600–4372 U/ml; they coincided with the clinical manifestations, as in our patient.⁸⁻¹⁰

The spontaneous synthesis of IgE in patients with the hyper-IgE syndrome is modulated in vivo largely by lymphokines such as IL-4, IL-5, and interferons (IFN) gamma and alpha, and by T and B cell cognate interactions.¹¹ In particular, IL-4 is essential to the synthesis of IgE induced in vitro in human T cell clones and their supernatants, whereas IFN γ seems to have an inhibitory role.¹² It is likely that the considerably increased production of IL-4, as detected in cultured PBMCs, enhanced the IgE levels in our patient. The serum IgE concentration returned to normal during her

disease remission, parallel to the decrease in her IL-4 concentration. We believe that our failure to detect circulating IL-4 may have been the result of an absence of free IL-4, or paracrine release of IL-4.¹³

The increased release of soluble CD23, a soluble form of the Fc portion of IgE (Fc ϵ R2/CD23), has been found in sera and supernatants from patients with connective tissue diseases such as rheumatoid arthritis.¹⁴ The expression of CD23 and the release of soluble CD23 are upregulated by IL-4, and promote IgE synthesis, though we did not measure them in this patient. The clinical significance of the increased concentrations of IL-4 and IgE in patients with AOSD remains unknown, but the combination of IL-4 and IgE played a major part in this patient's febrile episodes. While the aetiology of AOSD remains to be elucidated, the detailed evaluation of cases similar to that of our patient may provide clues to the understanding of the pathophysiology of this disease.

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