

Letter to the Editor

Hyper-IgE syndrome associated with an IL-4-producing γ/δ^+ T-cell clone

To the Editor:

The hyper-IgE syndrome is a rare immunodeficiency characterized by recurrent skin and pulmonary abscesses, eczema, and markedly increased levels of IgE in serum. In addition to immunologic abnormalities, patients also often exhibit abnormalities in dentition, bones, and connective tissues, suggesting that the hyper-IgE syndrome is a multi-system disorder.¹ Evaluation of the families in a cohort of 30 patients with the hyper-IgE syndrome demonstrated autosomal dominant inheritance,¹ but a causative gene has not been identified. Recently, a novel form of hyper-IgE syndrome with autosomal recessive inheritance has been described. The underlying gene defect of this variant, which is not associated with skeletal or dental abnormalities, is again unknown.^{2,3}

We report the case of a 30-year-old man, in whom we had diagnosed hyper-IgE syndrome at the age of 6 years.⁴ He has experienced multiple skin, perianal, and liver abscesses, as well as several episodes of pneumonia. He also has coarse facial features, scaphocephaly, and osteopenia. All primary teeth were retained and required extraction to allow permanent teeth to erupt. The serum IgE levels were up to 4840 kU/L. Since 1987, serum IgE levels varied between 1122 and 2800 kU/L (Fig 1). IgG₂ levels were decreased, but other Ig levels were in the normal range. Eosinophil numbers were initially high, but after surgical removal of a pulmonary aspergilloma in 1990, they were no longer increased. The patient has been continuously treated over the years with flucloxacillin and intravenous immunoglobulin preparations. These clinical and laboratory findings are typical of the hyper-IgE syndrome.

In some patients with the hypereosinophilic syndrome, IL-5-producing clonal T cells are believed to drive the inflammatory response.^{5,6} IL-4 and IL-13 are critical cytokines for IgE production. Therefore we hypothesized that, at least in some patients, the hyper-IgE syndrome is associated with the expansion of clonal T cells producing IL-4, IL-13, or both. In 1998, we performed immunophenotyping of the patient's blood lymphocytes and found that approximately 25% of the CD3⁺ T cells were both CD4⁺ and CD8⁺ (Fig 2, A). We also noticed that the CD4⁺ CD8⁺ T cells expressed slightly more CD3 compared with the other T cells. This abnormality provided the opportunity to further characterize these cells by means of a simple 2-color immunofluorescence flow cytometric technique.^{6,7} The abnormal double-negative T cells expressed the γ/δ T-cell receptor (Fig 2, A) but were α/β negative. Subsequent Southern blot analysis of the gene coding for the β chain of the T-cell receptor demonstrated the existence of a T-cell clone (Fig 2, B). The clonality of the T-cell expansion was also confirmed by analyzing the γ chain of the T-cell receptor with a PCR technique.

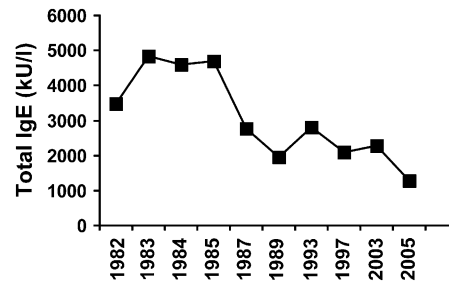


FIG 1. Long-term follow-up of serum IgE levels in a patient with hyper-IgE syndrome.

Further immunophenotyping of the patient's blood lymphocytes revealed that the aberrant T cells had high expression of CD25, HLA-DR, and CD71, suggesting previous activation *in vivo*, but did not express CD95. The T cell-associated molecules CD2, CD5, CD6, and CD7 were expressed, although surface staining for CD5 and CD7 was somewhat less compared with that for the CD4⁺ and CD8⁺ T-cells. In addition, we analyzed cytoplasmic cytokine levels in the aberrant T cells by means of double-immunofluorescence analysis with anti-T-cell receptor γ/δ and anticytokine antibodies. The γ/δ^+ T cells expressed high levels of IL-4 but no IL-5 (Fig 2, A). In addition to IL-5, we also observed no detectable levels for IL-2, IL-10, IL-13, and IFN- γ .

This case report suggests that cytokine-producing clonal T cells might not only occur in the hypereosinophilic syndrome but that they might also be involved in the pathogenesis of other chronic inflammatory disorders. Whereas IL-5 is a critical cytokine in eosinophilic responses, it is likely that the IL-4 generated by the double-negative γ/δ^+ T cells contributed to the extremely high IgE production in our patient. Therefore it seems that clonal T cells determine the type of inflammatory response by their cytokine production. Moreover, our data suggest that hyper-IgE syndrome might not always represent an inherited disorder.¹⁻³

It is unknown whether such clonal T cells arise in reaction to inflammation. It is possible that the lack of CD95 expression, which was associated with apoptosis resistance after stimulation with an agonistic anti-CD95 antibody *in vitro* (data not shown), contributed to the expansion of the γ/δ^+ T cells in the patient described here. We have now monitored the patient for almost 8 years and observed no significant changes regarding the numbers of aberrant T cells, serum IgE levels, and clinical features. Thus the disease appears to be stable, and we have no evidence for a transition into a T-cell lymphoma. However, because clonal T cells in the hypereosinophilic syndrome have been described as precursors of malignant T cells,^{6,8} regular immunomonitoring of such patients is recommended.

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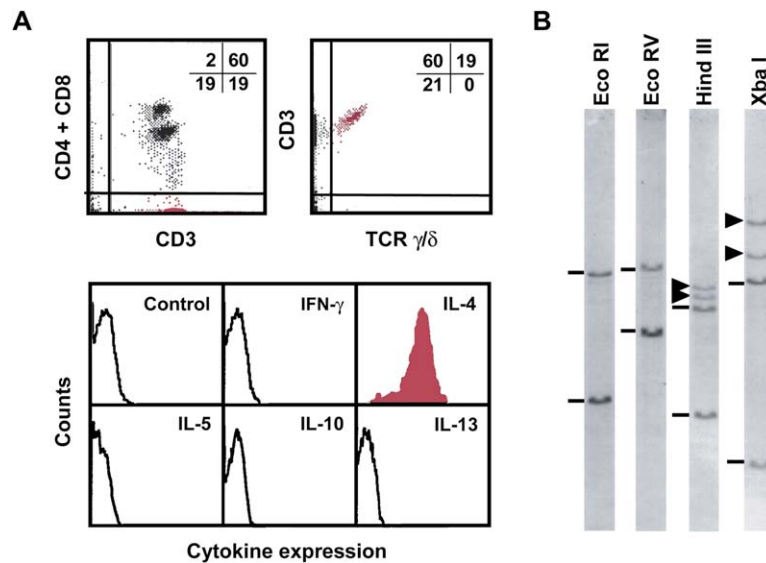


FIG 2. Identification of clonal T cells with an aberrant immunophenotype producing IL-4 in a patient with hyper-IgE syndrome. **A**, Increased proportion of $CD3^{+}CD4^{-}CD8^{-}$ T cells (marked in red; normal values, <3%). The CD3 fluorescence intensity on these cells was higher compared with that on the $CD4^{+}$ and $CD8^{+}$ T cells of the same patient (*left upper subpanel*), and these cells were T-cell receptor (TCR) γ/δ positive (*right upper subpanel*). The γ/δ^{+} T cells expressed high levels of IL-4 but not IFN- γ , IL-5, IL-10, or IL-13 (*lower subpanels*). **B**, Southern blot analysis of the gene coding for the β chain of the T-cell receptor. DNA derived from PBMCs was digested with *EcoRI*, *EcoRV*, *HindIII*, and *XbaI* restriction endonucleases, respectively. The *arrowheads* indicate the position of the rearranged alleles, and the *lines* indicate the position of the germ-line bands in normal cells.

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