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An unusual case of severe combined immunodeficiency with hypereosinophilia

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Investigation of the cytokine profile in a 26-year-old man, suffering from combined immunodeficiency with hypereosinophilia, revealed high levels of interleukin-4 and interleukin-5 and relatively low levels of interleukin-2 and interferon gamma, consistent with a T-helper type 2 pattern, as has been reported in Omenn's syndrome. However, some distinct clinical and immunological features suggest that this case may represent a unique disease with specific pathogenesis.

Keywords: hypereosinophilia, immunodeficiency, interferon gamma, Omenn's syndrome.

Introduction

In 1965, Omenn described a syndrome of severe combined immunodeficiency and hypereosinophilia [1]. This genetic disorder, which is usually fatal in the first year of life, is characterized by erythroderma, hepatosplenomegaly, diarrhoea, recurrent infections and failure to thrive. Immunological studies show hypereosinophilia, hyperIgE and diminished T cell proliferation in response to mitogenic and antigenic stimuli [2]. The pathogenesis is not yet elucidated [3].

Disorders with hyperIgE and/or hypereosinophilia, are reported to be associated with increased activity of type 2 helper T (Th2) lymphocytes, which secrete interleukin-4 (IL-4) and interleukin-5 (IL-5), combined with a decreased activity of type 1 helper T cells, which produce interleukin-2 (IL-2) and interferon gamma (IFN-γ) [4, 5]. This Th2 pattern was recently described in a young girl with Omenn's syndrome [6]. Here, we report an adult patient with severe combined immunodeficiency with hypereosinophilia, that appeared to have the same aberrant cytokine profile, but with distinct clinical features.

Case report

A 26-year-old man was evaluated in our clinic because of his unexplained immunological disorder. He was the third child of healthy unrelated parents. The first years of life were characterized by recurrent respiratory tract infections, mainly caused by pneumococci and Haemophilus influenzae. Variable hypereosinophilia and hyperIgE were noted. He developed a marked restriction in pulmonary function, and bilateral interstitial abnormalities on chest roentgenograms. At the age of eight, he suffered from a pneumococcal meningitis, and three years later from a presumed viral meningitis.
He developed widespread mollusca contagiosa and experienced the first of many (>15) episodes of varicella zoster infections. An exsudative dermatitis of the groins and a mucocutaneous candidiasis evolved. At the age of 19, severe candidalendophthamitis necessitated enucleation of the left eye. He suffered from varicella zoster pneumonia, and had several episodes of bilateral interstitial pneumonia, one time proven to be due to Pneumocystis carinii. Treatment elsewhere with prednisone and interferon alpha had produced a variable effect on eosinophil count, but no apparent effect on clinical and immunological status.

On physical examination, he was small for age (1.55 m), and had multiple mollusca, mucocutaneous candidiasis, and dermatitis of the groins; no lymphadenopathy or hepatosplenomegaly were found. Laboratory tests were compatible with previous results: marked hypereosinophilia (eosinophil count fluctuating between 2.7 and 57.8 \times 10^9 \text{L}^{-1}, normal <0.7 \times 10^9 \text{L}^{-1}), hyperIgE (IgE level 22 000 IU \text{mL}^{-1}, normal <100 \text{IU mL}^{-1}), defective proliferative response of peripheral blood mononuclear cells (PBMC) to mitogens (including phytohemagglutinin, concanavalin A and pokeweed mitogen) and antigens (including Candida, tetanus toxoid and tuberculin), and absent response to alloantigens. Delayed hypersensitivity skin tests were negative. The absolute lymphocyte and platelet count were normal (1.34 \times 10^9 \text{L}^{-1} and 164 \times 10^9 \text{L}^{-1}, respectively), as were the serum concentrations of IgG (12.6 g L^{-1}), IgM (0.99 g L^{-1}) and IgA (2.26 g L^{-1}). The serum levels of allohemagglutinins were low (1:4), as well as specific antibodies to pneumococcus, varicella and Haemophilus influenzae B (1, 0 and 1 U mL^{-1}, respectively); in vivo a serological response to these antigens was absent. Analysis of PBMC by flow cytometry immunophenotyping revealed a normal number of B cells (CD19 14%), but a diminished number of circulating T cells (CD3 32%, CD4 22% and CD8 11%), with normal CD4 CD8 ratio and normal proportions of CD45RA (‘naive’) and CD45R0 (‘memory’) CD4+ cells. The high number of DR- cells (33%) indicated activated T cells. The expression of the \alpha\beta and \gamma\delta TCR heterodimer amongst CD3+ cells was normal (27% and 3%). Function of the classical pathway complement system (CH50), granulocytes (phagocytosis killing and superoxide production) and natural killer cells was unaffected. Purine synthesis was normal. Chromosominal analysis indicated a normal male karyotype (46 XY).

Cytokine concentrations as determined by immunoenzymatic assays revealed the following. The serum level of IL-5 was very high (114 pg mL^{-1}, normally undetectable). Purified CD4+ cells cultured in the presence of PMA and A23187, produced a low amount of IFN-\gamma and abnormally high amounts of IL-4 and IL-5 compared to the cells of normal subjects (Fig. 1). This pattern of lymphokine secretion is characteristic of Th2-like cells. Because of the inhibiting effect of IFN-\gamma on the in vivo development of Th2 clones \cite{7}, we undertook a therapeutic trial with IFN-\gamma (Immukine, Boehringer Ing., Alkmaar, The Netherlands).

**Interferon-\gamma treatment**

With increasing doses of IFN-\gamma (up to 200 \mu g day^{-1}), a dramatic decrease in eosinophil count to 0.5 \times 10^9 \text{L}^{-1} was noted. However, improvement in proliferative response did not occur, and the serum level of IgE and IL-5 remained abnormally high (14,000 IU mL^{-1} and 126 pg mL^{-1}, respectively). The percentage of circulating T cells was still low and no change in T cell subsets was observed. The in vitro secretion of IL-4 and IL-5 clearly diminished, but this was accompanied by a fall in the in vitro production of IL-2 and IFN-\gamma (Fig. 1). Analysis of the cytokine profile performed on stimulated PBMC produced the same results, indicating that IFN-\gamma treatment did not restore IL-2 and IFN-\gamma production by the nonCD4+ cells. IFN-\gamma was stopped after 14 weeks. The patient

\[ \text{Fig. 1 In vitro production of cytokines by CD4+ cells, stimulated for 24 h with A23187 and PMA, from the patient before (-IFN\gamma) and after eight weeks (+IFN\gamma) treatment, and from four healthy controls. The scale units are IU mL^{-1} for IL-2 and IFN-\gamma, pg mL^{-1} for IL-4 and pg mL^{-1} \times 10^3 for IL-5. Error bars represent SEM.} \]
This Th2-type pattern has been reported previously in association with Omenn’s syndrome [6]. Although the described case shares clinical similarities with Omenn’s syndrome, there are distinct clinical and immunological features. The patient lacks the typical erythoderma, lymphadenopathy and organomegaly as described in Omenn’s syndrome, and his survival into adulthood is exceptional. Perhaps more importantly, the normal expression of the αβ and γδ TCR heterodimer and the absence of Β chain rearrangement favour against a restricted use of αβ or γδ T cell receptor genes – considered to be a major feature of the Omenn’s syndrome [3]. Neither did we detect clonal expansion of T cell lymphocytes as observed in previous cases [8].

In trying to classify our patient, several other immunodeficiencies should be considered. An abnormal cytokine profile with enhanced IL-4 and reduced IFN-γ production has been described in the Hyper-IgE ('Job's') syndrome [9]. However, the absence in our patient of the typical physiognomy, the lack of serious infections with Staphylococcus aureus and the profound disturbance of cellular immunity, as well as the extreme eosinophilia, render this diagnosis very unlikely. The clinical manifestations of the Wiscott–Aldrich syndrome appear to be more compatible, and defective IFN-γ and IL-2 production has been observed [10], but our patient lacks the typical defective expression of CD43 on the lymphocytes and has no thrombocytopenia. The normal expression of the DR antigen and the TCR CD3 complex excludes MHC class II deficiency (formerly called bare lymphocyte syndrome) and CD3(γ/ε) deficiency, respectively. The defective response of the patient’s CD4+ cells to receptor-independent stimulation with phorbol ester and a calcium ionophore argues against a defect in receptor-mediated intracellular signal transduction, as in CD8 deficiency (also called ZAP-70 deficiency) [11].

This case of combined immunodeficiency with hypereosinophilia, elevated IgE level and a Th2-like cytokine profile is reminiscent of Omenn’s syndrome, but the distinct clinical and immunological features suggest a unique disease with specific pathogenesis.

References

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