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 dermatis
of the groins and a mucocutaneous candidiasis
evolved. At the age of 19, severe candidalendophthamit-
is necessitated enucleation of the left eye. He suffered from varicella zoster pneumonia, and
had several episodes of bilateral interstitial pneumo-
nia, 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, mucocuta-
neous candidiasis, and dermatitis of the groins; no
lymphadenopathy or hepatosplenomegaly were
found. Laboratory tests were compatible with previ-
ous results: marked hypereosinophilia (eosinophil
count fluctuating between 2.7 and 57.8 × 10⁹ L⁻¹,
normal <0.7 × 10⁹ L⁻¹), hyperIgE (IgE level
22 000 IU mL⁻¹, normal <100 IU mL⁻¹), defective
proliferative response of peripheral blood mononu-
clear cells (PBMC) to mitogens (including phyto-
hemagglutinin, 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 × 10⁹ L⁻¹ and 164 × 10⁹ 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 pneu-
 mococcus, 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
('naïve') and CD45R0 ('memory') CD4⁺ cells. The
high number of DR⁺ cells (33%) indicated activated T
cells. The expression of the αβ and γδ 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.

Chromosomal analysis indicated a normal male
karyotype (46 XY).

Cytokine concentrations as determined by immu-
noenzymatic assays revealed the following. The
serum level of IL-5 was very high (114 pg mL⁻¹, nor-
mally undetectable). Purified CD4⁺ cells cultured in
the presence of PMA and A23187, produced a low
amount of IFN-γ and abnormally high amounts of
IL-4 and IL-5 compared to the cells of normal sub-
jects (Fig. 1). This pattern of lymphokine secretion
is characteristic of Th2-like cells. Because of the
inhibiting effect of IFN-γ on the in vivo development
of Th2 clones [7], we undertook a therapeutic trial
with IFN-γ (ImmuKine, Boehringer Ing., Alkmaar,
The Netherlands).

**Interferon-γ treatment**

With increasing doses of IFN-γ (up to 200 µg day⁻¹),
a dramatic decrease in eosinophil count to
0.5 × 10⁹ 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 vivo
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-γ (Fig. 1). Analysis of the cytokine
profile performed on stimulated PBMC produced the
same results, indicating that IFN-γ treatment did not
restore IL-2 and IFN-γ production by the nonCD4⁺
cells. IFN-γ was stopped after 14 weeks. The patient

![Fig. 1](https://example.com/fig1.png)

**Fig. 1** In vitro production of cytokines by CD4⁺ cells, stimulated for
24 h with A23187 and PMA, from the patient before (-IFNγ) and
after eight weeks (+IFNγ) treatment, and from four healthy
controls. The scale units are IU mL⁻¹ for IL-2 and IFN-γ, pg mL⁻¹
for IL-4 and pg mL⁻¹ × 10⁻⁴ for IL-5. Error bars represent SEM.
is currently doing well on a supportive regimen with fluconazole, cotrimoxazole, folic acid and intravenous immunoglobulins.

**Discussion**

In this case of severe combined immunodeficiency with elevated serum IgE and episodes of extreme hypereosinophilia, the helper T lymphocytes were found to produce large amounts of IL-4 and IL-5, and comparatively low amounts of IL-2 and IFN-γ. 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 erythrodema, 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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