An unusual case of severe combined immunodeficiency with hypereosinophilia

E. TH. M. DAMS*, F. MASCART-LEMONE*, L. SCHANDENÉ* & J. W. M. VAN DER MEER*

From the *Department of Internal Medicine, University Hospital Nijmegen, Nijmegen, The Netherlands and the 1 Department of Immunology, Hôpital Erasme, Brussels, Belgium


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 contagiosum 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 candidalendophthamititis 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 \( \times 10^3 \) L\(^{-1} \)), hyperlgE (IgE level 22 000 IU mL\(^{-1} \), normal <100 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 \( \times 10^3 \) L\(^{-1} \) and 164 \( \times 10^3 \) 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. Chromosomal 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 [7], we undertook a therapeutic trial with IFN-\( \gamma \) (Immuikine, 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 \( \times 10^3 \) 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-\( \gamma \) (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...
is currently doing well on a supportive regimen with
fluconazole, cotrimoxazole, folic acid and intra-
venous 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
erthroderma, lymphadenopathy and organomegaly
as described in Omenn’s syndrome, and his survival
into adulthood is exceptional. Perhaps more impor-
tantly, the normal expression of the αβ and γδ TCR
heterodimer and the absence of β chain rearrange-
ment favour against a restricted use of αβ or γδ T cell
receptor genes – considered to be a major feature of
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 abnor-
mal 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 com-
patible, 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 lympho-
cyte syndrome) and CD3(γ/δ) deficiency, respectivley.
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)

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

1. Omenn GS. Familial reticuloendotheliosis with eosinophilia.

2. Businco L, Di Fazio A, Grazia Zirulolo M, Boner AL, Valletta EA,
Ruco LP et al. Clinical and immunological findings in four infants with Omenn’s syndrome: a form of severe combined
immunodeficiency with phenotypically normal T cells, elevated
IgE, and eosinophilia. *Clin Immunol Immunopathol* 1987;
**44**: 123–33.

N, Journet O, Brousse N et al. Restricted heterogeneity of T lymphocytes in combined immunodeficiency with hypereosinophilia

4. Robinson DS, Quatayba H, Sun Y, Tsicopoulos A, Barkans J,
Bentley AM et al. Predominant Th2-like bronchoalveolar T-
lymphocyte population in atopic asthma. *New Engl J Med* 
1992; **326**: 298–304.

5. Cogan E, Schandéné L, Crusiaux A, Cochaux P, Vélu T,
Goldman M. Brief report: clonal proliferation of type 2 helper
T cells in a man with the hypereosinophilic syndrome. *New

6. Schandéné L, Ferster A, Mascart-Lemone F, Crusiaux A,
Gérard C, Marchant A et al. T helper type 2-like cells and ther-
apeutic effects of interferon-γ combined immunodeficiency
with hypereosinophilia (Omenn’s syndrome). *Eur J Immunol* 
1993; **23**: 56–60.

7. Scott P. IFN gamma modulates the early development of Th1
and Th2 responses in a murine model of cutaneous leishmaniasis.

8. Melamed I, Cohen A, Roifman CM. Expansion of CD3
CD4 CD8 T cell population expressing high levels of IL-

I et al. Shifts in interleukin-4 and interferon-γ production by T
cells of patients with elevated IgE levels and the modulatory
effects of these lymphokines on spontaneous IgE synthesis. *J

10. Paganelli R, Capobianchi MR, Ensoli B, D’Offizi GP, Facchini J,
Dianzani F, Aiuti F. Evidence that defective gamma interferon
production in patients with primary immunodeficiencies is
due to intrinsic incompetence of lymphocytes. *Clin Exp

Pathogenesis and treatment. *Clin Immunother* 1996; **5**:
137–60.

Received 3 March 1997; accepted 10 April 1997.

**Correspondence:** E. Th. M. Dams MD, Department of Internal
Medicine, University Hospital Nijmegen, PO Box 9101, 6500 HB
Nijmegen, The Netherlands (fax: +31 24 3541734; e-mail: E.
Dams@nugen@azn.nl).