

Th2-type cytokines, hypereosinophilia, and interleukin-5 in HIV disease

INTERLEUKIN (IL)-5 is a T-cell-, mast-cell-, and eosinophil-derived cytokine with selective effect on cells of the eosinophil lineage (1). Its role is debatable in experimental models of bronchial hyperresponsiveness, where it is linked to induction of IgE responses in mice, as well as in human asthma (2). Some recent reports could not be included in the review published in *Allergy* (1996) (3), and their results should be considered in

The hypereosinophilia and high IgE levels in HIV disease may be reversible due to changes in CD4/CD8 dynamics and viral infection.

view of studies on other conditions involving hypereosinophilia. Indeed, the original paper (4) describing Th2-type cells as inducers of eosinophilia in the primary eosinophilic syndrome did not identify prototypic Th2 (i.e., CD4+) T cells, but a rather rarer type of T-cell expansion, a CD4+/CD3- population, which we identified in a patient suffering from Sézary syndrome, a cutaneous T-cell lymphoma, with leukemic dissemination, showing eosinophilia, high serum IgE levels, and dermatitis in skin areas not directly involved by lymphoma (unpublished data, E. Scala). This source of IL-5 is not acknowledged in the review (3).

A recent paper (5) on the expansion of CD3+CD4-CD8- T cells producing IL-5 in primary hypereosinophilic syndromes in two patients, one with HIV infection, prompted us to report one other such case we detected with AIDS (stage IVC1 of the CDC classification) and a hyper-IgE-like syndrome (6). Eosinophilia was found in our patient (11-18% on repeated estimations, absolute number 605-950/ μ l), with diffuse pruritic dermatitis showing hyperpigmentation and lichenification from the head to the limbs. He was being treated with the antiretroviral drug zidovudine, and cotrimoxazole for *Pneumocystis carinii* pneumonia pre-

vention. Discontinuation of this treatment (for fear of drug intolerance), as well as administration of antihistamines (cetirizine and hydroxyzine) and steroids (prednisone and deflazacort), did not reduce the itching. Serum levels of IgE ranged between 580 and 1524 kU/l. We examined the phenotype of peripheral blood lymphocytes from this patient, and the *in vitro* production of cytokines by T cells and clones. The CD4+ cell count decreased from 215 to 9 cells/ μ l, and a T-cell line grown from this patient in rIL-2 showed only 1% CD4+ T cells, with 59% CD8+ T cells and 38% CD4-CD8-TCR $\alpha\beta$ + lymphocytes. When this line was cloned, no CD4+ T-cell clones were grown. Sixty-nine T-cell clones were screened after 4-week *in vitro* culture with rIL-2. The phenotype of the clones and their pattern of cytokine production are reported in Table 1.

CD8+ lymphocytes exerting Th2-like activity on B-cell production of IgE have been reported. The unexpected and still unreported finding in this patient was the increased presence of a subpopulation of double-negative (CD4-CD8-) T cells. This subset (4-14% of the circulating T cells) was a high IL-4 and IL-5 producer. The observation that "dim" CD8+ clones also produced Th2-type cytokines seems to indicate that part of the apparently massive switch of cytokine production may be related to loss of the CD8 molecule, as previously described (7). However, most CD8 brightly expressing T-cell clones also showed a shift to IL-4 and IL-5 production. Therefore, the relative increase of a subpopulation of double-negative T cells may account only in part for the development of hyper-IgE and eosinophilia in this patient. Fas expression in this case was not investigated, but no report on Fas expression by eosinophils has appeared so far (5).

Table 1. TCR $\alpha\beta$ + T-cell clones from patient: phenotype and function. No CD4+ single-positive T-cell clones were grown. Dim staining of CD8+ cells was assessed after electronic gating on TCR $\alpha\beta$ + cells. Th type of cytokines was based on IL-4 and interferon- γ secretion after 48-h restimulation with anti-CD3 and phorbol esters, measured by ELISA on supernatants (detection limit: 7.5 pg/ml for IL-4 and 80 pg/ml for IFN- γ). IL-5 was produced by 90% of clones also in absence of IL-4

Phenotype	n	Th1	Th0	Th2
CD4-CD8+ ^{bright}	49	8	20	21
CD4-CD8+ ^{dim}	11	2	3	6
CD4-CD8-	8	0	4	4
CD4+CD8+	1	0	1	0
All clones	69	10	28	31

In three T-cell clones of the double-negative phenotype, we measured the *in vitro* production of chemokines of the C-C type, and we found high amounts secreted (12–28 ng/ml for RANTES, 21–48 ng/ml for MIP-1 α , and 10–64 ng/ml for MIP-1 β), independently of the Th type of the clones. The stable presence of this double-negative Th2 type subset has not been assessed by other studies. The patient survived after 3 years' observation, and spontaneously recovered from the hyper eosinophilia and the symptoms described, after reintroduction of antiretroviral treatment. Studies of his T-cell function are in progress, but the CD4+ cell number further decreased, thus pointing to the possible role of this cell in the hyper eosinophilic syndrome observed. The high production of C-C chemokines in an AIDS patient with hyper eosinophilia may be due to various causes, but it is very unlikely to have been due to antiviral defense mechanisms (8). C-C chemokines act as potent activators of eosinophils, and may be implicated in allergic manifestations (9).

Our observation highlights two main points:

- 1) CD4-CD8- T cells may be important sources of IL-5 and other type 2 cytokines, as well as chemokines involved in eosinophil recruitment and activation
- 2) hyper eosinophilic (hyper-IgE) syndrome in HIV disease may be reversible as a result of subpopulation dynamics and viral infection.

Of course, these points are relevant to other observations on the primary hyper eosinophilic syndrome without HIV infection.

Key words: CD8; CD4; cytokines; eosinophilia; HIV disease; hyper-IgE; Th2 cells.

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Adverse reaction to potassium iodide from a cough syrup

IODIDE-containing drugs are effective and are widely used in enhancing sputum clearance when given orally to patients with mucus hypersecretion. Iodides appear to stimulate secretion of airway fluid directly, and these agents can also probably stimulate a vagal reflex that causes a mucokinetic effect (1).

Toxicity resulting from ingestion of excess iodine has not been commonly reported. Nevertheless, some patients are known to have allergic-type reactions to iodine (2, 3).

Iodides have been implicated in the pathogenesis of many dermatologic diseases (4–6), usually after application of an antiseptic solution, and rarely after systemic administration of iodine.

■ A 66-year-old man was referred to our department for allergologic study because of adverse drug reactions. His medical history included chronic obstructive lung disease, blood hypertension, and penicillin allergy. Our patient had presented an episode of angioedema, itching, and erythema involving the face and neck, together with dyspnea, a few hours after taking the second dose of a cough syrup (Elixifilin®) containing theophylline (80 mg/15 ml) and potassium iodide (130 mg/15 ml). Its additives include saccharose (2.25 g/15 ml) and ethanol (10%).

Those symptoms disappeared 24 h after treatment with parenteral corticosteroids, and avoidance of such cough syrups.

An oral challenge test with Elixifilin, as is, was performed (single-blind and placebo-controlled). Increasing doses were taken hourly by our pati-

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