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Clinical and Immunological Features of Patients with Interleukin-5-Producing T Cell Clones and Eosinophilia

Hans-Uwe Simon[a] Sabine Gisela Plötz[b] Dagmar Simon[c]
Reinhard Dummer[d] Kurt Blaser[e]

[a]Department of Pharmacology, University of Bern, Switzerland; [b]Division of Environmental Dermatology and Allergy GSF/Technical University of Munich, Germany; [c]Department of Dermatology, University of Bern, [d]Department of Dermatology, University of Zürich, and [e]Swiss Institute of Allergy and Asthma Research (SIAF), University of Zürich, Davos, Switzerland

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Clonal T cells · Eosinophils · Hypereosinophilia · Immunophenotype · Interleukin-5

Abstract
Recent work suggests that in some patients with the hypereosinophilic syndrome, a clone of abnormal T cells produces large amounts of interleukin-5. In this study, we examined 60 patients with idiopathic eosinophilia. Sixteen patients had circulating T cells with an aberrant immunophenotype that, in most cases, were associated with different forms of skin inflammation. The abnormal T cells produced large amounts of interleukin-5, which may have increased eosinophil differentiation in the bone marrow of these patients.

Idiopathic Eosinophilia Is Frequently Associated with Clonal T Cells Which Express an Aberrant Immunophenotype

Among 60 patients with persistent eosinophilia of unknown origin, we identified 16 patients who demonstrated significant numbers of interleukin-5-producing T cells with an abnormal immunophenotype in their blood [1]. In 50% of the cases, the diagnosis 'clonal T cell expansion' was confirmed by the demonstration of identical T cell receptor rearrangements. Out of these 16 patients, 8 fulfilled the diagnostic criteria of a hypereosinophilic syndrome [2]. None had a detectable parasitic or HIV infection. Cardiac complications were not observed. A subgroup of patients demonstrated elevated total IgE levels, but only 1 patient suffered from an IgE-mediated allergic disease (allergic asthma). Table 1 summarizes the hematological and immunological findings of these patients. It is likely that the interleukin-5 production by the aberrant T cells is responsible for increased eosinophil differentiation in the bone marrow of these patients (fig. 1). In contrast, the pathogenesis behind the T cell expansion is unclear, but may include both increased T cell growth [3] and decreased T cell apoptosis [4].

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Correspondence to: Prof Hans-Uwe Simon
Department of Pharmacology, University of Bern
Friedbühlstrasse 49
CH–3010 Bern (Switzerland)
Tel. +41 31 632 32 81, Fax +41 31 632 49 92, E-Mail hus@pki.unibe.ch

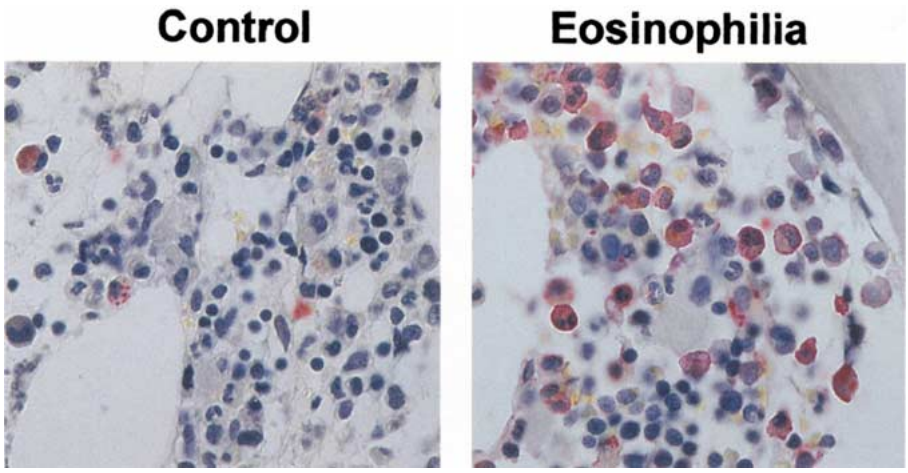


Fig. 1. Numbers of mature eosinophils are increased in patients with idiopathic eosinophilia. Eosinophils were stained with anti-eosinophilic cationic protein monoclonal antibody (EG1) by immunohistochemistry (APAAP technique).

Table 1. Hematological and immunological laboratory findings

Patient No.	Leukocytes mm^{-3}	Eosinophils %	Lymphocytes %	CD3+ CD4+ %	CD3+ CD8+ %	CD4/CD8 ratio	CD3– CD16+ %	CD19+ %	Aberrant T cells, % lymphocytes	Short description of the immunophenotype of the aberrant T cells
1	11,300	24.5	35.0	69.8	15.8	4.4	7.6	2.5	21.3	CD2low CD3+ CD4+ CD5low CD25+ CD95+
2	10,100	44.0	38.5	55.0	10.5	5.2	3.0	0.5	18.0	CD3+ CD4– CD8– CD5– CD25+ CD95+
3	8,300	38.5	32.0	31.9	16.0	2.0	7.3	7.3	33.9	CD3– CD4+ CD5high CD25+ CD95+
4	9,100	27.0	18.0	47.1	29.9	1.6	10.0	4.9	16.0	CD3+ CD4+ Vβ5a+ CD25+ CD95+
5	13,200	9.0	15.5	23.7	37.1	0.6	10.3	14.8	6.5	CD3+ CD8+ CD6high CD25– CD95–
6	12,400	8.5	71.0	90.0	7.0	12.8	2.0	0.5	70.0	CD2– CD3+ CD4+ CD25+
7	8,700	38.0	27.5	42.2	9.9	4.3	20.6	3.0	17.5	CD3– CD4low CD5high CD25+ CD95+
8	7,900	11.0	27.0	11.7	49.3	0.2	12.3	9.2	19.7	CD2low CD3low CD8high CD6low CD7low CD25– CD95–
9	13,500	43.0	6.0	73.6	11.5	6.4	4.8	3.9	14.5	CD3+ CD4+ CD7– Vβ5c+ CD25+ CD95+
10	10,600	30.0	23.0	83.3	8.9	9.4	3.1	1.9	50.0	CD3+ CD4+ CD25+ CD95–
11	5,100	26.0	17.0	25.0	15.6	1.6	10.9	19.2	25.0	CD3+ CD4– CD8– CD25– CD95–
12	10,300	44.0	18.0	62.0	26.7	2.2	4.2	2.6	55.8	CD3low CD4low CD6low CD7– CD25+ CD95–
13	10,110	23.0	13.0	55.1	16.9	3.3	11.5	6.3	18.3	CD2high CD3+ CD4+ CD6low CD7– CD25+ CD95+
14	10,300	49.0	8.0	59.9	32.9	1.8	2.9	1.9	32.9	CD3low CD4+ CD5low CD6low CD7– Vβ6.7+ CD25+ CD95–
15	4,100	32.5	18.0	35.7	7.5	4.7	18.6	11.7	20.0	CD3+ CD4+ CD5high CD7– CD25+ CD95+
									25.0	CD3+ CD4– CD8– CD25+ CD95–
16	12,000	23.0	47.5	24.0	29.2	0.8	20.0	17.3	22.0	CD3+ CD8+ CD5low CD7low CD25– CD95–

Lineage (CD2, CD3, CD4, CD5, CD6, CD7, CD8)- and activation-associated (CD25, HLA-DR, CD95) T cell surface molecule expressions were measured on peripheral blood lymphocytes by two-color immunofluorescence analysis.

Clonal T Cells Are Associated with Different Forms of Skin Inflammation

Fourteen out of the 16 patients demonstrated pruritic skin lesions including erythroderma (fig. 2A), widespread reddish papules (fig. 2C), urticarial plaques (fig. 2E) or poikiloderma. Skin histology revealed perivascular infiltrates with lymphocytes and eosinophils with various degrees of epidermal involvement (fig. 2B, D, F). The reason(s) for the different pattern of skin symptoms despite apparently similar disease causes remain to be investigated. In only 3 patients, some histological features of cutaneous T cell lymphoma were observed [5]. Many patients were treated with prednisone because of fluctuating symptoms and eosinophilia. In all cases, bone marrow was densely infiltrated with mature eosinophils (fig. 1), without granulomas or evidence of cancer.

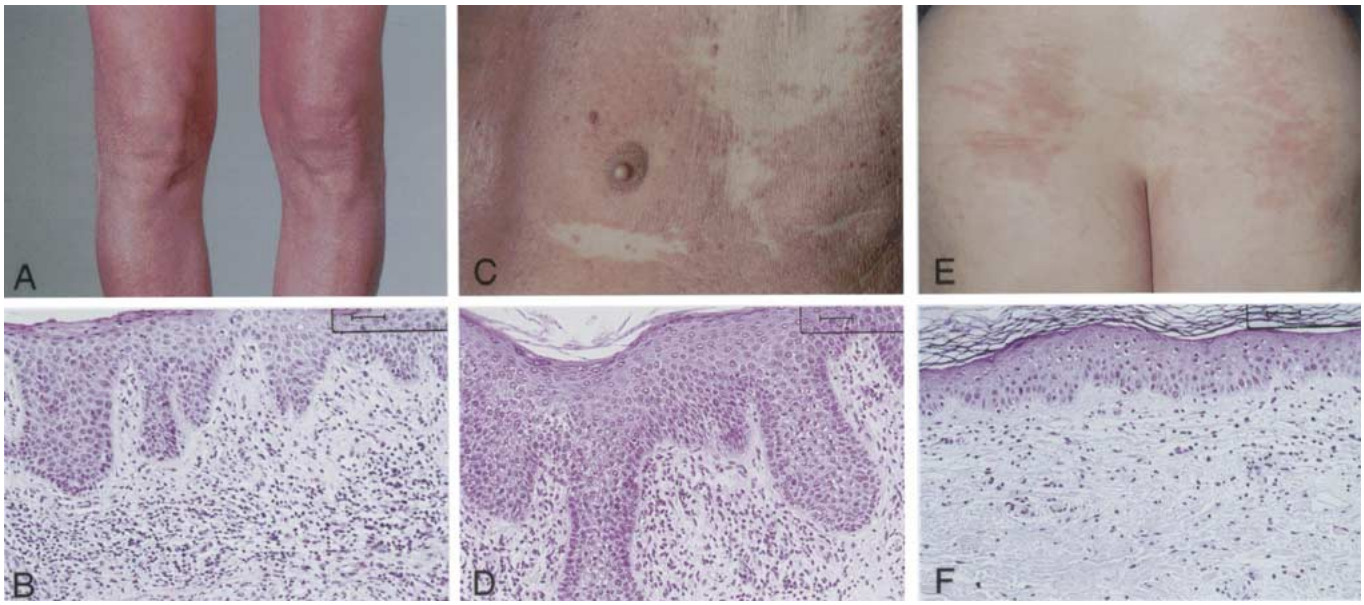


Fig. 2. Typical clinical and histological cutaneous features of patients with idiopathic eosinophilia. **A**, **B** Pruritic erythroderma of patient 4 (see table 1). **C**, **D** Reddish papules of patient 13. **E**, **F** Urticarial plaques of patient 3 persisting for days. Histology: hematoxylin-eosin; bar represents 50 μm.

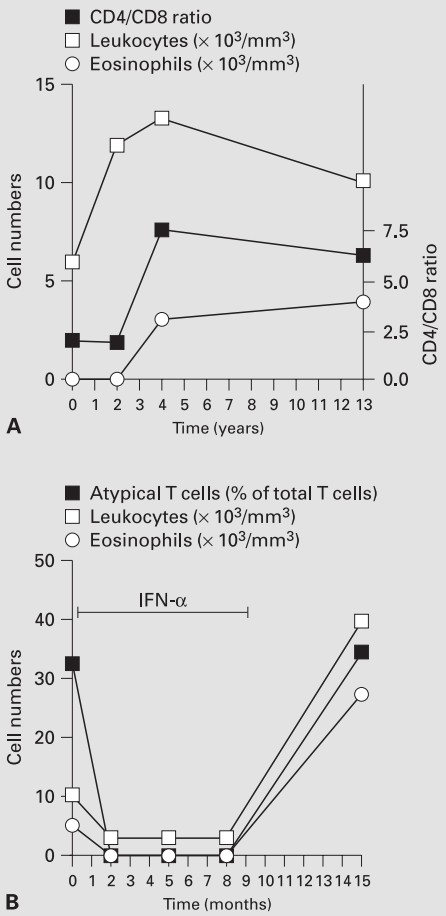
Immunological Monitoring of Blood Lymphocytes Reflects Therapeutic Effects and Transition into Malignant Lymphoproliferation

We performed follow-up studies on single patients over several years. As shown in figure 3A, 1 patient (patient 9) was studied for more than 13 years. In the first 2 years after the onset of the disease with pruritic poikiloderma, both the number of eosinophils as well as the CD4/CD8 ratio of peripheral blood lymphocytes were within a normal range. Two years later, the CD4/CD8 ratio as well as the number of peripheral blood eosinophils had dramatically increased and remained constant for more than 9 years. A test for the presence of clonal rearrangements of the γ-chain, done 8 years after the initial skin symptoms, was negative. Five years after this PCR test, the diagnosis of monoclonal T cell expansion was established by flow cytometry.

The possibility of identifying clonal T cells due to their aberrant immunophenotype also makes their quantification during therapeutic interventions possible. As shown in figure 3B, therapy with interferon-α2b (Intron®) was associated with a complete disappearance of the atypical clonal T cells within a few weeks (patient 14). This suggests that immunomonitoring provides a powerful tool to determine the effectiveness of a certain therapy. The patient remained relapse-free over a time period of about 9 months. Then, due to exacerbation of skin symptoms, the treatment with interferon-α was stopped. T cells with the same aberrant immunophenotype expanded again (fig. 3B). Malignant T cell lymphoma was subsequently diagnosed. The diagnosis was based on the histology of a lymph node biopsy. The transition of a premalignant disease into a malignant T cell lymphoma was also observed in two additional patients (patients 2 and 12) and was always associated with a rapid increase in the numbers of leukocytes, lymphocytes, abnormal T cells and eosinophils in peripheral blood. However, the mechanisms of this transition from relatively benign into a malignant lymphoproliferative disorder remain to be determined.

Conclusions

Expansion of T cells expressing an aberrant immunophenotype is frequently observed in patients with idiopathic eosinophilia. Because these cells can be distinguished from normal T cells due to altered lineage-associated markers, it is possible to identify and quantify them in blood. Interestingly, not only CD4+ but also CD8+ T cells may expand and cause eosinophilic syndromes. At least in cases where the abnormal T cells lack the death



receptor CD95, defective T cell apoptosis might play a role in the pathogenesis of T cell expansion, because CD95 ligand/CD95 molecular interactions have been demonstrated to be essential in the control of lymphocyte homeostasis [6]. Since the expanded T cells have the potential to transform into malignant cells, they should therefore represent the major target for therapeutic interventions in these patients.

Acknowledgments

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Fig. 3. Occurrence of clonal T cells correlates with the numbers of eosinophils. **A** Long-term follow-up of patient 9. The diagnosis of clonal T cell expansion was established 13 years after the appearance of the first skin symptoms. The increase in peripheral blood eosinophil numbers was associated with a clear increase of the CD4/CD8 ratio. The situation remained practically unchanged over a time period of 9 years. **B** Immunomonitoring of patient 14. The patient's disease was diagnosed as a hypereosinophilic syndrome. The occurrence of aberrant T cells as the likely cause of the hypereosinophilia was established by flow cytometry (see table 1). The same investigation was repeated 2 weeks later and revealed identical data. The patient was subsequently treated with interferon-α2b (IFN-α, 9×10^6 IU, 3 times a week, s.c.). The T cells with an aberrant immunophenotype completely disappeared. The numbers of eosinophils dramatically decreased in parallel. Due to exacerbation of skin symptoms, the IFN-α treatment was stopped after 9 months, and the patient developed a malignant T cell lymphoma. The newly expanding T cells had the original aberrant immunophenotype.

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