Chronic Eosinophilic Leukaemia Presenting with Erythroderma, Mild Eosinophilia and Hyper-IgE: Clinical, Immunological and Cytogenetic Features and Therapeutic Approach

A Case Report


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Key Words
Chronic eosinophilic leukaemia · Erythroderma · Hyper-IgE translocation t(5;12)(q33;p13)

Abstract
A 23-year-old, white male metallurgist presented with pruritic erythematous maculo-papules over the trunk and upper limbs and 6 months later developed erythroderma, eosinophilia and multi-organ dysfunction. A diagnosis of chronic eosinophilic leukaemia was made on the basis of myeloproliferative involvement of both peripheral blood and bone marrow, associated with eosinophilic differentiation and a t(5;12)(q33;p13) translocation. The initial therapeutic approach was interferon alfa-2b plus cytosine arabinoside, for 13 months, followed by hydroxyurea plus vincristine. There was improvement of skin lesions, disappearance of eosinophilia and decrease of serum immunoglobulin E, towards normal values.

Introduction
The idiopathic hypereosinophilic syndrome (HES) has been defined as a disease characterized by unexplained eosinophilia (greater than $1.5 \times 10^9/l$) persisting for at least 6 months and leading to organ damage. The diagnosis of HES is usually based on the exclusion of any underlying disease that could be responsible for the eosinophilia and the lack of any evidence of clonality of myeloid cells. At present there is accumulating evidence that many cases that were previously considered as HES are either reactive conditions or clonal eosinophilic disorders [1–4]. Persistent reactive eosinophilia may occur in a number of disease states including allergy, parasitic infections and neoplastic conditions. Accordingly, reactive eosinophilia has been reported in various skin diseases (eczema, dermatitis, drug reactions), malignancies (Hodgkin’s disease, T-cell lymphoma, lung cancer), chronic granulomatous diseases (tuberculosis), fungal infections (coccidiodomycosis, aspergillosis) and drug reactions [5].
Chronic Eosinophilic Leukaemia

A distinct myeloproliferative disorder characterized by prominent eosinophilic differentiation is currently recognized, and usually designated as chronic eosinophilic leukaemia (CEL) [1]. Accumulating evidence suggests that CEL is not a single disease, but comprises a variety of different myeloproliferative disorders (MPD), which have in common the proliferation of a neoplastic clone of cells with prominent eosinophilic differentiation. These include chronic myelomonocytic leukaemia with eosinophilia (CMML-Eo) and chronic myelomonocytic leukaemia with eosinophilia and evolution into acute myeloid leukaemia and T-lineage lymphoblastic lymphoma (CMML-Eo/AML/T-ALL) [4]. Interestingly, specific chromosomal aberrations have been related to CEL syndromes. CMML-Eo is frequently associated with the t(5;12)(p13;q13) and other translocations involving chromosome 5q31–35 [6–8] whereas CMML/Eo/AML/T-ALL cases have been associated with t(8;13)(p11;q12) and other cytogenetic abnormalities involving chromosome 8p11–12 [9, 10]. Other chromosomal abnormalities that have been occasionally associated with CEL are t(8;9)(p22;p23) [11], t(3;9;5)(q25;q34;q33) [12] and trisomy 15 [3]. In some of the reported cases, the molecular mechanisms involved in the translocations have been identified [13–17]. Eosinophilia may also occur in other clonal stem cell disorders, such as other specific chronic myeloproliferative disorders, myelodysplastic syndromes and acute myeloid leukaemia. Once again, recurrent chromosomal translocations have been documented in these patients, suggesting that eosinophilic differentiation occurs as a consequence of certain specific cytogenetic abnormalities [3, 18].

From a clinical point of view, the differential diagnosis between HES and CEL is not always clear. Patients with CEL more frequently display hepatosplenomegaly, which might be associated with neutrophilia, monocytosis, anaemia, thrombocytopenia or trilineage myelodysplasia. Neutrophil alkaline phosphatase is often reduced and transformation into an acute leukaemia has been reported in some patients [8].

Although present in CEL, erythroderma may also be a manifestation of allergy, parasitic infection and non-haemopoietic malignant conditions [19].

Herein, we describe a patient with a past history suggestive of allergy that presented with erythroderma, leucocytosis with mild eosinophilia, increased IgE and organomegaly, and whose cytogenetic findings established the diagnosis of a CEL. To the best of our knowledge, this is the first case in whom an association of erythroderma, increased IgE, eosinophilia and a clonal myeloproliferative disorder with eosinophilic differentiation has been reported.

Case Report

A 23-year-old white male metallurgist was referred to the Dermatology Department of Hospital São João (Porto, Portugal) in April 1998 because of persistent pruritic erythematous maculo-papules over the trunk and upper limbs; these had been present for 1 year. Full blood counts were: WBC 34.0 × 10⁹/l, haemoglobin (Hb) 12.6 g/dl; platelets 137 × 10⁹/l (with platelet clumps). The patient was started on prednisolone, 40 mg/day, per os, with gradual tapering till December 1998.

At this stage, he was referred to the Haematology Department, because of generalized skin lesions and organomegaly. He complained of pruritus and dry eyes and physical examination showed extensive maculopapular skin lesions and generalized exfoliative erythroderma, keratoconjunctivitis sicca, periocular xanthomas, deep subcutaneous cervical induration, generalized lymphadenopathy and enlarged liver and spleen. Ophthalmologic examination revealed bilateral perilimic infiltration. Skin prick tests were strongly positive for house dust mite. A presumptive diagnosis of contact dermatitis was made, based solely upon an occupational history of handling of chromium products, given the infeasibility of skin contact tests with these specific materials. His full blood count was: WBC 14.0 × 10⁹/l, neutrophils 6.2 × 10⁹/l, eosinophils 1.5 × 10⁹/l, basophils 0.28 × 10⁹/l, lymphocytes 4.2 × 10⁹/l, monocytes 0.14 × 10⁹/l, metamyelocytes 0.14 × 10⁹/l, red cell count 3.55 × 10¹²/l, Hb 11.1 g/dl, reticulocytes 4%, platelets 200 × 10⁹/l, erythrocyte sedimentation rate 98 mm. Neutrophil alkaline phosphatase activity was decreased. Serum IgE levels were markedly increased: 3,003 kU/l (normal range: <114 kU/l), while other serum immunoglobulins were: IgG 1,810 mg/dl (normal range: 650–1,500 mg/dl); IgA 604 mg/dl (normal range: 78–312 mg/dl); IgM 192 mg/dl (normal range: 604 mg/dl). Circulating immune complexes were mildly elevated: 4.7 μg/dl (normal range: <3.3 μg/dl).

The bone marrow aspirate and trephine biopsy showed marked hypercellularity and very striking granulocytic and eosinophilic hyperplasia, increased mast cells and increased megakaryocytes which were pleomorphic and dysplastic. Both skin and lymph node biopsies showed eosinophilic infiltration.

A flow cytometric study of peripheral blood T lymphocytes based on four-colour staining with a large panel of monoclonal antibodies against various T-cell-associated antigens did not reveal any immunophenotypic abnormality that would have suggested a clonal T-cell disorder. The immunophenotypic analysis study of the TCR Vβ repertoire and the molecular study of the TCRβ gene similarly excluded this possibility.

Immunophenotypic studies confirmed the presence of eosinophils in the peripheral blood, which represented 18.4% of the total leucocytes. Like normal eosinophils, these cells showed marked green-to-red autofluorescence and were positive for CD13+, CD34+dim, CD65+, CD11b+ and CD15+ myeloid-associated antigens; they coexpressed the CD38+dim and CD45+. In contrast, they lacked reactivity for CD2, CD3 (both membrane and cytoplasmic), CD4, CD5, CD7, CD8, CD10, CD19, CD20 and CD79a lymphoid-
related antigens and markers associated with cell immaturity (CD34, HLA-Dr and terminal deoxynucleotidyl transferase). Other myeloid antigens (MPO, CD14, CD61, glycophorin A) were negative. This phenotype is identical to that usually reported for normal peripheral blood eosinophils.

Chromosomal analysis, carried out after short-term culture of bone marrow cells, showed 46 XY, t(5;12)(q33;p13) [2], 46 XY [2] (fig. 1); t(9;22) was excluded by RT-PCR using specific primers for the BCR and ABL genes. t(5;12) has been reported to fuse the TEL/ETV6 gene at 12p13 to PDGFßR at 5q33 [13]. We tested whether PDGFßR was also involved in this case by interphase FISH using flanking cosmid probes as previously described [20]. Of 73 evaluable interphase cells analysed, 50 (68%) showed one fused signal and separated red and green signals confirming that the PDGFßR gene was indeed disrupted.

Based on the cytogenetic findings, a diagnosis of CEL was made and the patient was started on interferon alfa-2b (7,500,000 units 3 times/week) plus cytosine arabinoside (20 mg daily subcutaneous). This therapeutic approach was successful in decreasing the WBC count and peripheral blood neutrophilia, eosinophilia and basophilia, and the bone marrow hypercellularity; there was also a reduction in the hepatomegaly, splenomegaly and lymphadenopathy. However, by July 1999, during the course of this therapy, large nodules had appeared on his face (2 × 1 cm) and forearms (3 × 4 cm); prednisolone (40–80 mg every second day per os) was then added. After 12 months of therapy, the patient still had skin lesions, increased IgE and circulating immune complexes. He was then started on hydroxyurea (1,000 mg/day per os) plus vincristine (2 mg i.v., days 1 and 8 of 28), which was efficacious in controlling the eosinophilia and ameliorated organ infiltration; the facial skin infiltration lessened as did the periorcular xanthomas. After 5 months of therapy, organomegaly was no longer detectable.

At that time, his laboratory results were as follows: WBC 2.8 × 10⁹/l (neutrophils 1.74 × 10⁹/l, eosinophils 0.07 × 10⁹/l, basophils 0.02 × 10⁹/l, lymphocytes 0.77 × 10⁹/l, monocytes 0.16 × 10⁹/l), serum IgE 1,149 kU/l, IgG 1,730 mg/dl, IgA 732 mg/dl and IgM 111 mg/dl. A bone marrow aspirate (while on hydroxyurea) showed a marked improvement in the granulocytic, eosinophilic and megakaryocytic hyperplasia; megaloblastic changes were noticeable, especially in the erythroid compartment; dysplastic features were still present, mainly involving the megakaryocytic lineage. Cytogenetic analysis revealed no t(5;12) positive metaphase out of 30 analysed. Biopsy of both erythematous and apparently normal skin showed slight perivascular dermal infiltration by lymphoid cells. Immunohistochemical studies performed on these biopsy specimens showed somewhat heavier infiltration by both CD4+ T cells (199 versus 100 cells/mm²) and eosinophils (5 vs. 0 cells/mm²) in the erythematous areas. In contrast, no differences were observed in the number of mast cells or in BCL-2 staining.

**Discussion**

We report the case of a 23-year-old man with CEL presenting with atypical clinical features that led to a differential diagnosis with other conditions associated with erythroderma, increased serum IgE and persistent eosinophilia.

The fact that allergy could have explained a large proportion of the initial clinical and laboratory findings together with positive skin prick test for house dust mite and a history of occupational exposure to metals led us to...
consider the possibility of a reactive eosinophilia secondary to a contact dermatitis. However, some of the clinical and laboratory manifestations occurring during the initial follow-up period, including the evidence of widespread tissue infiltration by eosinophils, strongly argued against this possibility. Two patients described by Keene et al. [21] who had cytogenetic abnormalities involving 12p13 within eosinophils also proved to simultaneously have schistosomiasis. The intriguing question is whether or not a reactive process could have contributed to the development of a clonal proliferation of eosinophils. It might be speculated that in this patient an atopic tendency could, by an unknown mechanism (e.g. cytokine production), have been a predisposing factor to the myeloproliferative disorder. Erythroderma and increased serum IgE have both been described in association with T-cell lymphomas and other clonal T-cell disorders [22–28]. These conditions were therefore considered in the differential diagnosis. However, T-cell clonality was excluded by both immunophenotypic analysis of peripheral blood lymphocytes and molecular analysis of the TCR Vß repertoire and the TCRß gene, respectively.

The clinical and laboratory findings in HES and CEL overlap. In this case, cutaneous, ocular and immunological manifestations suggested HES, whereas the occurrence of organomegaly and the cytological features of the bone marrow aspirate favoured the diagnosis of a myeloproliferative disorder. The cytogenetic findings were essential in establishing the diagnosis of CEL, by disclosing the t(5;12)(q33;p13), a clonal marker which has previously been reported in association with eosinophilic differentiation in a myeloproliferative disorder. Despite this, the immunophenotypic features of the peripheral blood eosinophils present in this patient were identical to those reported for normal peripheral blood eosinophils [29].

From the therapeutic point of view, the diagnosis of CEL had important implications. Although there is no consensus as to the best therapeutic approach, corticosteroids, hydroxyurea and interferon-alpha have been used with variable success [10–12, 30], complete remissions being described with interferon therapy [12, 30]. In the case herein reported, complete remission was not achieved with any of these therapeutic strategies. However, there was a marked clinical and laboratory improvement. This patient is now being considered for bone marrow transplantation in the hope of eliminating the leukemic clone and curing the disease.

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References


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