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αIFN-induced hematologic and cytogenetic remission in chronic eosinophilic leukemia with t(1;5)

LUIGIA LUCIANO, LUCIO CATALANO, CLAUDIA SARRANTONIO, ANNA GUERRIERO, CATELLO CALIFANO, BRUNO ROTOLI
Department of Hematology, Federico II University, Naples, Italy

ABSTRACT

Chronic eosinophilic leukemia (CEL) is a myeloproliferative disease characterized by excessive eosinophilic proliferation with clonal cytogenetic abnormalities. The most frequent cytogenetic abnormality is a break in the q 31-35 region of chromosome 5, where genes encoding for IL-3, IL-5 and GM-CSF (all cytokines involved in eosinophilopoiesis) are located. We report the case of a patient with CEL with t(1;5) (q23;q31), who obtained complete hematologic and major cytogenetic response after two years of α-interferon (α-IFN) therapy. Two other cases of complete response to α-IFN are reported in the literature. A trial with α-IFN could be considered as front line treatment in this rare disease.

Key words: hypereosinophilic syndrome, chronic eosinophilic leukemia, 5 q31-33, α-interferon

Idiopathic hypereosinophilic syndrome (HES) is a syndrome characterized by marked (>1500/μL) and prolonged (>6 months) eosinophilia with no identifiable cause, often associated with organ damage, especially to the heart. The syndrome may represent a heterogeneous group of diseases, among which the distinction of a truly malignant process from more frequent non malignant proliferations may be difficult.[1] Several reports have shown the presence of chromosomal abnormalities in patients with typical HES, suggesting a clonal origin for these cases, thus identifying a distinct myeloproliferative disorder: chronic eosinophilic leukemia (CEL).[2-5]

A number of specific chromosome abnormalities have been found in association with CEL, including trisomies and translocations, the latter often involving chromosome 5, where genes encoding for cytokines such as IL3, IL5, and GM-CSF are located. Although CEL patients may have a chronic disease with a prolonged course, blastic transformation may occur;[5] thus, proper treatment is needed to prevent or delay such a catastrophic event. The efficacy of α-interferon (α-IFN) in CML has induced some authors to test this drug in a few CEL patients:[3,5,6] hematologic and, in at least two cases, cytogenetic remission was obtained.[3,6] We report a case of CEL with t(1;5) translocation, in which treatment with α-IFN resulted in long term survival with a major cytogenetic response.

Correspondence: Prof. Bruno Rotoli, MD, viale Augusto 148, 80125 Naples, Italy.
Phone: international +39-081-7462037 – Fax: international +39-081-7462165.

Case Report

An asymptomatic 21-year old man was found to have moderate leukocytosis with eosinophilia during a routine examination in April 1991; no cause for secondary eosinophilia was identified. In October 1991 the patient was referred to our unit. Past medical history was totally irrelevant. At that time physical examination showed moderate enlargement of the spleen (5 cm below the costal margin) with no liver enlargement or lymphoadenopathy. The white blood cell count was 21.6×10^9/L, with eosinophils 8×10^9/L; Hb was 1.64 g/L and platelets 190×10^9/L. The leukocyte alkaline phosphatase score was normal. Bone marrow aspirate showed hypercellularity with intense myeloid hyperplasia and increased eosinophils (30%); a moderate dysplasia (abnormal basophilic granules, ring hole nuclei, vacuolization) was also observed (Figure 1). A cytogenetic analysis, performed on 24 h unstimulated bone marrow culture, showed a 46XY t(1;5)(q23 q31) karyotype in 28/29 metaphases observed; in many instances the presence of typical eosinophilic granules surrounding the chromosomes (Figure 2) testified that the metaphases belonged to eosinophilic cells. A diagnosis of eosinophilic leukemia was made. Since the patient had no symptoms, he received no treatment during the following 6 months. In April 1992 splenomegaly, leukocytosis (WBC 35×10^9/L), eosinophilia (21.1×10^9/L) and bone marrow eosinophils all increased; cytogenetic analysis confirmed t(1;5) in 18/18 metaphases. A fluorescent *in situ* hybridization (FISH) examination using a whole chromosome 5-specific paint probe (CAMBIO, Cambridge, England), supported the cytogenetic result (Figure 3). The patient started α-IFN therapy (Intron-A, Schering-Plough, Italy) at a dose of 3 million units three times a week. The treatment was well

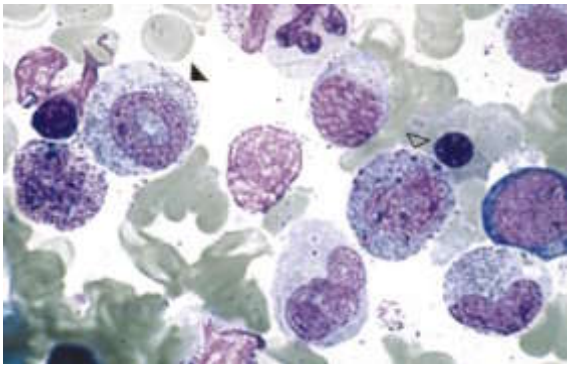

Figure 1. Increased eosinophils and dysplastic findings in bone marrow at diagnosis.
▲= a ring hole nucleus; △= basophilic granules in an eosinophilic cell.

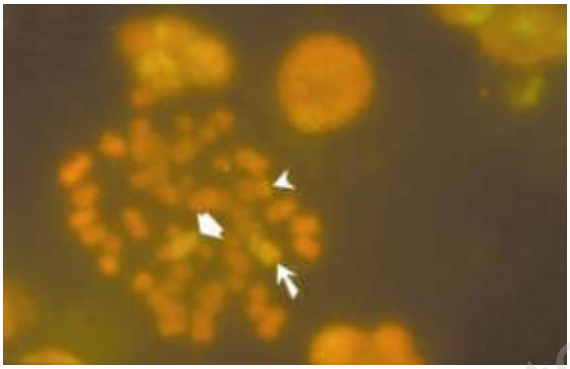

Figure 3. The translocation (1;5) is clearly detected by FISH using a whole chromosome 5-specific paint probe: ⇨ the normal chromosome 5; ⇨ the altered chromosome 5 with an unpainted extremity; ▷ part of chromosome 5 is found on the partner chromosome 1.

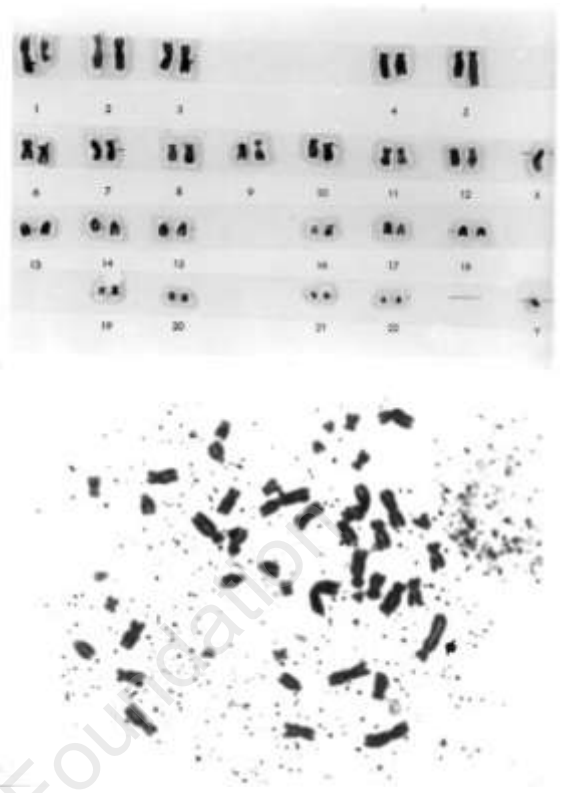

Figure 2. An abnormally long chromosome in a metaphase (a) identified as t(1;5) in the karyotype (b). The metaphase belongs to an eosinophilic cell, as demonstrated by the numerous eosinophilic granules surrounding the chromosomes.

tolerated and caused a decrease of WBC (13.5 $\times 10^9$/L) and eosinophils (6.95$\times 10^9$/L), and spleen size normalization. Eight months later the dose was increased to 9 MU three times a week. This schedule was maintained for two years and resulted in a hematologic remission with a major cytogenetic response (out of 15 metaphases observed, 4 were 46 XY t(1;5) and 11 were 46 XY). In September 1994 the patient was switched to a maintenance dose of 9MU twice a week. The latest follow-up, performed in March 1999, 7 years after diagnosis, showed normal WBC, mild eosinophilia (0.49$\times 10^9$/L), normal spleen size and persistent major cytogenetic response (out of 20 metaphases observed, 3 were 46 XY t(1;15) and 17 were 46 XY) . The patient is continuing α-IFN at maintenance dose.

Discussion

Chronic eosinophilic leukemia is a hypereosinophilic disorder characterized by clonal cytogenetic abnormalities. Chromosome abnormalities include trisomy of chromosome 8, 10[2,5] or 15,[5] monosomy of chromosome 7, loss of the Y chromosome[2,3] or translocations. The most frequent translocations are those involving the long arm of chromosome 5, with a number of different chromosome partners.[2,3,4,6] A frequent partner is the short arm of chromosome 12; patients with t(5;12) often show myeloproliferative/myelodysplastic features with normal peripheral blood eosinophil count and increased bone marrow eosinophils,[2] thus identifying a distinct disease entity.[7] Other possible partners are chromosome 1, 2, 3, 9, 11, 12q, 14 and 16. In these translocations the breakpoint on chromosome 5 was always in the region q31-q33. As in other promiscuous translocations (e.g., those involving 11q23 in ALL and 3q26 in NHL), the gene involved in the neoplastic transformation is obviously thought to be located on the specific chromosome rather than on the promiscuous partner. Thus, we may surmise that the breakpoint in the region q31-q33 of chromosome 5 plays a pathogenetic role in the development of CEL. In fact, in this region the genes encoding for IL-3, GM-CSF and IL-5 (all cytokines that stimulate eosinophil production) are located. IL-3 is required as an early-acting

factor, while IL-5 and GM-CSF as late-acting lineage-specific factors.[8] Moreover, IL-3, GM-CSF and IL-5 have additional activity on intermediate stages of eosinophilopoiesis, and they are also active on mature eosinophils.[9] The relevance of the role of IL-5 in eosinophilic differentiation is testified *in vivo* by patients with eosinophilia showing high serum IL-5 levels, in some instances proven to be secreted from the clonal population itself.[2] A chromosomal translocation may induce dysregulation of one or more of these genes, resulting in autocrine overproduction of cytokines.

There is no standard therapy for hypereosinophilic syndrome; treatment regimens have been directed to prevention of organ damage by eosinophil infiltration and to symptom relief. Different therapeutic agents have been used, such as prednisone, hydroxyurea, vincristine, etoposide, alkylating agents and cyclosporin A.[1] The efficacy of α-IFN has been widely demonstrated in CML.[10] In other chronic myeloproliferative disorders (CMD), such as essential thrombocythemia and polycythemia vera, α-IFN may be an effective treatment option. Some reports[11-13] have demonstrated the ability of α-IFN to induce cytogenetic remission in CMD other than CML. Thus, it is not surprising that α-IFN may induce hematologic and cytogenetic improvement also in CEL or HES. At variance to another report,[14] our data confirm at least two publications[3,6] regarding the efficacy of α-IFN in CEL. Thus, we think that a trial with α-IFN is to be considered front line therapy in this rare disease.

Contributions and Acknowledgments

LL, CS and AG performed the cytogenetic and FISH analyses; LC and CC conceived the clinical trial and did the hematologic work up. LL and BR wrote the paper.

The criteria for the order in which the name of the authors appears is based on the importance of their contribution to the study.

Disclosures

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