

Diagnosis of an Early Precursor-B–ALL Presenting With Hypereosinophilia Using FISH on Immunomagnetically Selected CD19+ Cells

Karl T. Hagler, MD
 Roberto T. Zori, MD
 Constance M. Yuan, MD, PhD
 Brian A. Gray, MS
 Jan S. Moreb, MD

*University of Florida
 Gainesville, Florida*

Case Report

A 21-year-old male college student presented with abdominal pain and cough. Complete blood count showed a white blood cell (WBC) count of 93,500 with 65% eosinophils. Hemoglobin and platelet counts were normal. Computed tomography showed pulmonary infiltrates and superior mesenteric vein thrombosis. Anticoagulation with heparin was initiated. Bronchoscopy with transbronchial biopsy showed eosinophilic infiltration. Fecal studies and serology for parasites were negative. The findings of superior mesenteric vein thrombosis and eosinophilic infiltration of the lungs were thought to be consistent with manifestations of hypereosinophilia.

Peripheral blood flow cytometry revealed marked eosinophilia and less than 1% precursor-B lymphoblasts. Bone marrow aspirate and biopsy showed 90% cellularity, with approximately 60% eosinophils. Flow cytometry identified 4% abnormal B-lymphoblasts that were CD34+, CD19+, CD20 variable, CD10+, and CD58+. Cytogenetic analysis by G-banding showed only a normal 46XY karyotype. Our tentative diagnosis was precursor-B–cell acute lymphoblastic leukemia (ALL) with hypereosinophilia that is usually associated with the t(5;14) chromosomal abnormality; however, due to the relative small population of leukemic cells in the marrow, cytogenetic analysis was negative. Therefore, we used magnetic beads coated with a monoclonal antibody to CD19 (Dynabeads M-450 CD19 [Pan B], Dynal Bio-

tech) to sort and enrich for the neoplastic cells. Cytogenetic analysis on the enriched cells was unsuccessful due to failure to yield metaphase cells. However, fluorescent in situ hybridization (FISH) using a commercially available dual color “break-apart” DNA probe (Vysis, Inc.) for the immunoglobulin heavy chain (IgH) region applied to the CD19+ enriched cells demonstrated an alteration of the IgH gene. Eleven of 225 (4.8%) interphase nuclei had separation of the DNA probe consistent with a translocation involving the IgH locus at the 14q32 region. In addition, 24 nuclei (10.7%) showed apparent loss of the distally labeled segment of the IgH probe, suggesting a secondary clonal event (Figure 1).

With this information, we initiated ALL-directed chemotherapy.¹ On day 28 of treatment, the patient’s WBC count was 5,600 with 0% eosinophils. Repeat bone marrow examination found variable cellularity (10–50%) and less than 1% precursor-B lymphoblasts by flow cytometry.

Discussion

ALL associated with eosinophilia is uncommon but well described in the literature.^{2–7} First described in 1973,⁸ recent reports have documented the presence of t(5;14)(q31;q32) translocation involving the IgH gene on chromosome 14 and the interleukin (IL)-3 gene on chromosome 5.^{2–4,7} The result is activation of the IL-3 gene, causing growth effects to promote eosinophilia.⁹ Patients are usually children or adolescents and often present with signs and symptoms of the hypereosinophilic syndrome due to eosinophilic organ infiltration. Organs involved are most commonly the heart, lungs, central nervous system, skin, liver, and spleen.¹⁰ As in our patient, thrombosis has also been reported.^{11,12} The differential diagnosis

Address correspondence to:

Jan S. Moreb, MD, University of Florida Department of Medicine, Division of Hematology/Oncology, PO Box 100277, Gainesville, FL 32610-0277; E-mail: morebjs@medicine.ufl.edu.

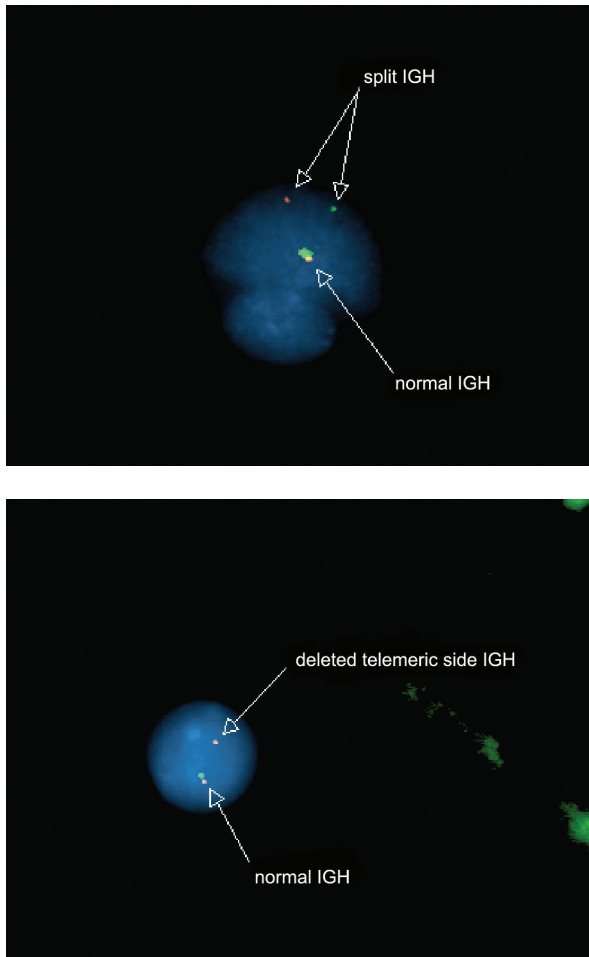


Figure 1. Interphase fluorescence in situ hybridization probes of CD19-enriched cell sample revealed 2 alterations. On top, there is a separation of the DNA probe of IgH gene, consistent with chromosomal translocation. Bottom, an apparent loss of the distally labeled portion of the immunoglobulin H probe.

of eosinophilia is extensive and, therefore, other causes of eosinophilia should be excluded. A comprehensive review of the eosinophilias has recently been published.¹⁰

The diagnosis of such disease often occurs later, as the eosinophilia may precede the full-blown presentation of ALL and may also herald relapse after therapy.¹⁰ Frequently, these patients are treated with steroids for the eosinophilia and its symptoms, while the diagnosis of ALL may be delayed by weeks to months.² The prognosis

and survival after treatment of these patients appear to be similar as compared to age and sex-matched ALL patients without eosinophilia.²

Here, we report a case of a patient with precursor-B-ALL and hypereosinophilia whose diagnosis was made difficult due to minimal numbers of leukemic cells at presentation. To help confirm the diagnosis in this case, we used immunomagnetic beads coated with monoclonal CD19 antibody to enrich bone marrow neoplastic cells for chromosomal analysis and FISH. While we were unable to demonstrate the $t(5;14)$ translocation, the combination of the clinical presentation and demonstration of an IgH alteration on chromosome 14 by FISH in CD19+ lymphoblasts were consistent with precursor-B-ALL and hypereosinophilia. The patient was treated with ALL-directed chemotherapy with good response. As illustrated in this case, the use of FISH with specific probes on an enriched cell population containing the blasts may expedite the diagnosis and treatment of these unique patients.

References

1. Linker CA, Levitt LJ, O'Donnell M, et al. Treatment of adult acute lymphoblastic leukemia with intensive cyclical chemotherapy: a follow-up report. *Blood*. 1991;78:2814-2822.
2. Hogan TF, Koss W, Murgu AJ, et al. Acute lymphoblastic leukemia with chromosomal 5;14 translocation and hypereosinophilia: case report and literature review. *J Clin Oncol*. 1987;5:382-390.
3. Grimaldi JC, Meeker TC. The $t(5;14)$ chromosomal translocation in a case of acute lymphocytic leukemia joins the interleukin-3 gene to the immunoglobulin heavy chain gene. *Blood*. 1989;73:2081-2085.
4. Baumgarten E, Wegner RD, Fengler R, et al. Calla-positive acute leukaemia with $t(5q;14q)$ translocation and hypereosinophilia—a unique entity? *Acta Haematol*. 1989;82:85-90.
5. Jain P, Kumar R, Gujral S, et al. Granular acute lymphoblastic leukemia with hypereosinophilic syndrome. *Ann Hematol*. 2000;79:272-274.
6. Fishel RS, Farnen JP, Hanson CA, et al. Acute lymphoblastic leukemia with eosinophilia. *Medicine (Baltimore)*. 1990;69:232-243.
7. Knuutila S, Alitalo R, Ruutu T. Power of the MAC (morphology-antibody-chromosomes) method in distinguishing reactive and clonal cells: report of a patient with acute lymphatic leukemia, eosinophilia, and $t(5;14)$. *Genes Chromosomes Cancer*. 1993;8:219-223.
8. Spitzer G, Garson OM. Lymphoblastic leukemia with marked eosinophilia: a report of two cases. *Blood*. 1973;42:377-384.
9. Meeker TC, Hardy D, Willman C, et al. Activation of the interleukin-3 gene by chromosome translocation in acute lymphocytic leukemia with eosinophilia. *Blood*. 1990;76:285-289.
10. Brito-Babapulle F. The eosinophilias, including the idiopathic hypereosinophilic syndrome. *Br J Haematol*. 2003;121:203-223.
11. Zylberberg H, Valla D, Viguie F, et al. Budd-Chiari syndrome associated with 5q deletion and hypereosinophilia. *J Clin Gastroenterol*. 1996;23:66-68.
12. Narayan S, Ezughah F, Standen GR, et al. Idiopathic hypereosinophilic syndrome associated with cutaneous infarction and deep venous thrombosis. *Br J Dermatol*. 2003;148:817-820.

Review

Daniel J. DeAngelo, MD, PhD

Dana-Farber Cancer Institute

Hagler et al report an unusual case of a 21-year-old male patient with profound hypereosinophilia. Through a rather laborious effort, the authors were able to deduce that the patient's peripheral blood eosinophilia was secondary to an underlying precursor-B-ALL. Through flow cytometric analysis, a small population of CD34-positive lymphoblasts that coexpressed CD10 and CD19 were detected.

The current case in study is remarkably similar to that described by Hogan and colleagues¹ and initially by Spitzer and Garson in 1973.² Hogan reported in his series that all three patients presented with a 14q cytogenetic abnormality and 2 patients had an identical t(5;14)(q?;q32) reciprocal translocation. As reported by Meeker et al,³ the fusion partner on chromosome 5 was subsequently localized to the IL-3 gene locus on chromosome 5q31. Making use of a "split-apart" IgH probe, the authors demonstrated a rearrangement of the IgH gene in 4.8% of the interphase nuclei approximating the percentage of abnormal cells identified using flow cytometric analysis. Although far from an ordinary case, the authors were able to deduce that the patient carried a diagnosis of a precursor-B-ALL giving rise to the extraordinary leukocytosis and marked eosinophilia, both of which resolved after definitive chemotherapy directed toward the patient's ALL.

The present case raises several interesting features, but the most salient is the evaluation of a patient with marked eosinophilia. An elevated eosinophil can be secondary to either a reactive process or a clonal myeloproliferative disorder. Idiopathic hypereosinophilic syndrome (IHES) is defined as an eosinophil count greater than $1.5 \times 10^9/L$ for greater than 6 months, often associated with organ infiltration that typically involves the skin, heart, lungs, or nervous system.^{4,5} The diagnosis of IHES can only be made in the clear absence of a reactive process. There are several nonmalignant conditions that have been associated with peripheral blood eosinophilia and these include infections, most commonly parasitic. In addition, allergic diseases such as asthma, atopic dermatitis or eczema have been associated with peripheral blood eosinophilia. Patients with Churg-Strauss syndrome can also develop eosinophilia. Allergic reactions to drugs such as carba-

mezapine, minocycline, or IL-2 infusions have been reported to cause a reactive eosinophilia that typically disappears when the drug has been discontinued. Other causes of eosinophilia include connective tissue diseases such as rheumatoid arthritis, Wegener granulomatosis, polyarteritis nodosum, and celiac disease. Occasionally, eosinophilia occurs only in the tissues and in the absence of peripheral blood findings. This is the case for Loeffler syndrome,⁶ eosinophilic fasciitis,⁷ and eosinophilic cellulites.⁸ It is important to note that the eosinophilia in these nonmalignant conditions is typically polyclonal.

Many malignant diseases have been associated with a nonclonal eosinophilic disorder. These malignancies include Langerhan cell histiocytosis as well as non-Hodgkin and Hodgkin lymphomas.⁹⁻¹¹ Some solid tumors, including renal cell, lung, breast, as well as cancers of the female genital tract, have also been associated with a reactive nonclonal eosinophilia.

It is important to differentiate between eosinophils resulting from a reaction to the underlying malignancy as compared to eosinophils that are part of the underlying malignant clone. Disorders of the latter type include systemic mast cell diseases (SMCD), specifically systemic mastocytosis with eosinophilia, which represents only a subset of patients with SMCD.¹²⁻¹⁵ These patients typically have elevated tryptase levels and have been found to respond to imatinib therapy.¹⁶ Many other chronic myeloproliferative disorders are associated with a clonal eosinophilia. These include chronic myeloid leukemia (CML) as well as chronic myelomonocytic leukemia (CMML). In CMML, a subset of patients have balanced translocations involving the platelet derived growth factor receptor (PDGFR) β gene.¹⁷ To date, 8 PDGFR β fusion partners (ETV6, CEV14, HIP1, H4/D10S170, RABEP1, Myomegalin/PDE4DIP, NIN, and HCMOGT-1) have been identified.¹⁸⁻²⁵ In each case, chromosomal translocation results in fusion of the 3' region of PDGFR β encoding the kinase domain to a 5' fusion partner with a putative oligomerization domain. It has been demonstrated in most of these that the PDGFR β tyrosine kinase is constitutively activated as a consequence of fusion to a dimerization or oligomerization motif in the amino-terminal partner. For example, fusion of the ETV6 PNT oligomerization domain to PDGFR β results in self-association and constitutive tyrosine kinase activity, and both the oligomerization and kinase domains are required for transformation of hematopoietic cells.

We recently described a patient with a myeloproliferative disorder characterized by the chromosomal abnormality t(5;14)(q33;q32).²⁶ The consequence of the chromosomal translocation is fusion of the coiled-

Address correspondence to:

Daniel J. DeAngelo, MD, PhD, Dana-Farber Cancer Institute, 44 Binney Street, Boston, MA 02115.

coil domain of KIAA5109 to the tyrosine kinase domain of PDGFR β . KIAA5109 is an uncharacterized gene with a predicted coiled-coil oligomerization domain with homology to the HOOK family of proteins. Imatinib therapy in this patient resulted in a rapid, complete, and durable hematologic and cytogenetic response.

In addition to the chronic myeloproliferative disorders, 2 specific subtypes of acute myelogenous leukemia (AML) are also associated with hypereosinophilia. These include the French, American, and British (FAB) classification of AML defined as M4Eo, characterized by inversion(16)(p13q22) or t(16;16)(p13;q22).²⁷ This inversion results in a chimeric fusion of the CBF- β and MYH11 genes. In addition, the AML subtype FAB-M2 is frequently characterized by a reciprocal translocation involving t(8;21)(q22;q22) which links the AML-1 and ETO genes and is often accompanied by peripheral blood eosinophilia.²⁸ La Starza and colleagues²⁹ described a clonal eosinophilia characterized in a patient with AML involving the ETV6 gene on chromosome 12p13 fused to the ABL gene on 9q34. ETV6 is an ETS translocation variant of TEL. As described above, the ETV6 gene has also been described in patients with CMML as described above, which fuses the PDGFR β gene on chromosome 5q33 to ETV6.¹⁷

Other abnormal karyotypes have been reported in patients with AML that are characterized by eosinophilia. These include monosomy 7, trisomy 1 and a variety of relatively rare translocations, which include t(10;11)(p14;q21), t(5;16)(q33;q22) and t(16;21)(p11;q22).³⁰⁻³⁴ In addition to patients with AML, an eosinophilic myelodysplastic syndrome characterized by a translocation involving t(1;7) has also been described.³⁵

Several case reports have described a pleuripotent hematopoietic stem cell disorder that typically presents as a myeloproliferative syndrome with eosinophilia. This syndrome, termed EMS, often transforms into a B-cell or more commonly a T-cell lymphoblastic lymphoma. Patients with this disease have been shown to have a translocation of the fibroblast growth factor (FGFR) 1 gene on 8p11 to the zinc finger protein ZNF198 on 13q12, although other fusion partners have also been described.³⁶⁻³⁸ We recently reported a patient who was successfully treated with PKC412, which is a staurosporine analog and a potent tyrosine kinase inhibitor with activity against the FMS-like tyrosine kinase receptor III (Flt-3).³⁹

Hagler et al describe a patient who presented with a leukocytosis and marked eosinophilia and was found to have a precursor-B-ALL. Although only reported in small case series, patients with the t(5;14)(q31;q32) translocation seem to have a similar prognosis when compared to other non-Philadelphia-chromosome-containing patients with precursor-B-ALL.³ The most important feature of

this case is that it clearly demonstrates the extreme importance of giving a substantial amount of diagnostic consideration to these various hematologic malignancies before attributing the peripheral blood eosinophilia to IHES.

We as well as those from other groups have recently characterized patients with a clonal eosinophilic disorder in which other clonal as well as nonclonal eosinophilic disorders have been excluded, a syndrome referred to as IHES or chronic eosinophilic leukemia (CEL).^{4,5} We and others have demonstrated that many patients with IHES contain a previously uncharacterized human gene FIP1-like-1 (FIP1L1) fused to PDGFR α .⁴⁰⁻⁴³ Patients with the FIP1L1-PDGFR α gene fusion respond to imatinib therapy at extraordinarily low levels. The IC₅₀ for imatinib using in vitro kinase inhibition assays was only 3 nM compared to approximately 600 nM for the BCR-ABL tyrosine kinase.⁴⁰ Therefore, the majority of patients can be successfully treated at doses of imatinib of 100 mg per day or even possibly lower. Interestingly, approximately 40% of patients who lack the FIP1L1-PDGFR α fusion protein also responded to imatinib therapy suggesting either genetic heterogeneity or a false-negative rate for our current polymerase chain reaction-based assay.

The goal of therapy in patients with hypereosinophilia as described by Weller and Bubley⁴⁴ was to prevent damage from infiltration of both reactive and clonal eosinophils. But as is evident in this case report, the elucidation of the etiology for the eosinophilia is of utmost importance. In this case, a malignant precursor-B-ALL was identified and successfully treated with appropriate chemotherapy. This case further illustrates the importance of an exhaustive workup in order to exclude reactive eosinophilia or eosinophilia as a part of an underlying malignant hematopoietic disorder before a diagnosis of IHES or CEL can be entertained. Although polymerase chain reaction analysis demonstrating the presence of the FIP1L1-PDGFR α fusion gene can be of extraordinary help in differentiating between IHES or SMCD with associated eosinophilia from other causes of eosinophilia, IHES still remains a diagnosis of exclusion. The treatment for both IHES and SMCD with eosinophilia is imatinib, especially for those patients with the presence of the FIP1L1-PDGFR α fusion gene, whereas the treatment for the other hematologic diseases associated with eosinophilia is disease-specific.

References

1. Hogan TF, Koss W, Murgo AJ, Amato RS, Fontana JA, VanScoy FL. Acute lymphoblastic leukemia with chromosomal 5;14 translocation and hypereosinophilia: case report and literature review. *J Clin Oncol*. 1987;5:382-390.
2. Spitzer G, Garson OM. Lymphoblastic leukemia with marked eosinophilia: a report of two cases. *Blood*. 1973;42:377-384.
3. Meeker TC, Hardy D, Willman C, Hogan T, Abrams J. Activation of the interleukin-3 gene by chromosome translocation in acute lymphocytic leukemia

- with eosinophilia. *Blood*. 1990;76:285-289.
4. Gotlib J, Cools J, Malone JM 3rd, Schrier SL, Gilliland DG, Coutre SE. The FIP1L1-PDGFR α fusion tyrosine kinase in hypereosinophilic syndrome and chronic eosinophilic leukemia: implications for diagnosis, classification, and management. *Blood*. 2004;103:2879-2891.
 5. Brito-Babapulle F. The eosinophilias, including the idiopathic hypereosinophilic syndrome. *Br J Haematol*. 2003;121:203-223.
 6. Slabbynck H, Impens N, Naegels S, Dewaele M, Schandevyl W. Idiopathic hypereosinophilic syndrome-related pulmonary involvement diagnosed by bronchoalveolar lavage. *Chest*. 1992;101:1178-1180.
 7. Shulman LE. Diffuse fasciitis with eosinophilia: a new syndrome? *Trans Assoc Am Physicians*. 1975;88:70-86.
 8. Bogenrieder T, Griese DP, Schiffner R, et al. Wells' syndrome associated with idiopathic hypereosinophilic syndrome. *Br J Dermatol*. 1997;137:978-982.
 9. Brugnoni D, Airo P, Tosoni C, et al. CD3-CD4+ cells with a Th2-like pattern of cytokine production in the peripheral blood of a patient with cutaneous T cell lymphoma. *Leukemia*. 1997;11:1983-1985.
 10. Kawasaki A, Mizushima Y, Matsui S, Hoshino K, Yano S, Kitagawa M. A case of T-cell lymphoma accompanying marked eosinophilia, chronic eosinophilic pneumonia and eosinophilic pleural effusion. A case report. *Tumori*. 1991;77:527-530.
 11. Endo M, Usuki K, Kitazume K, Iwabe K, Okuyama Y, Urabe A. Hypereosinophilic syndrome in Hodgkin's disease with increased granulocyte-macrophage colony-stimulating factor. *Ann Hematol*. 1995;71:313-314.
 12. Pardanani A, Brockman SR, Paternoster SF, et al. FIP1L1-PDGFR α fusion: prevalence and clinicopathologic correlates in 89 consecutive patients with moderate to severe eosinophilia. *Blood*. 2004;104:3038-3045.
 13. Tefferi A, Pardanani A. Systemic mastocytosis: current concepts and treatment advances. *Curr Hematol Rep*. 2004;3:197-202.
 14. Tefferi A, Pardanani A. Clinical, genetic, and therapeutic insights into systemic mast cell disease. *Curr Opin Hematol*. 2004;11:58-64.
 15. Pardanani A, Reeder T, Li CY, Tefferi A. Eosinophils are derived from the neoplastic clone in patients with systemic mastocytosis and eosinophilia. *Leuk Res*. 2003;27:883-885.
 16. Klion AD, Noel P, Akin C, et al. Elevated serum tryptase levels identify a subset of patients with a myeloproliferative variant of idiopathic hypereosinophilic syndrome associated with tissue fibrosis, poor prognosis, and imatinib responsiveness. *Blood*. 2003;101:4660-4666.
 17. Golub TR, Barker GF, Lovett M, Gilliland DG. Fusion of PDGF receptor beta to a novel ets-like gene, tel, in chronic myelomonocytic leukemia with t(5;12) chromosomal translocation. *Cell*. 1994;77:307-316.
 18. Abe A, Emi N, Tanimoto M, Terasaki H, Marunouchi T, Saito H. Fusion of the platelet-derived growth factor receptor beta to a novel gene CEV14 in acute myelogenous leukemia after clonal evolution. *Blood*. 1997;90:4271-4277.
 19. Ross TS, Bernard OA, Berger R, Gilliland DG. Fusion of Huntingtin interacting protein 1 to platelet-derived growth factor beta receptor (PDGF β R) in chronic myelomonocytic leukemia with t(5;7)(q33;q11.2). *Blood*. 1998;91:4419-4426.
 20. Kulkarni S, Heath C, Parker S, et al. Fusion of H4/D10S170 to the platelet-derived growth factor receptor beta in BCR-ABL-negative myeloproliferative disorders with a t(5;10)(q33;q21). *Cancer Res*. 2000;60:3592-3598.
 21. Schwaller J, Anastasiadou E, Cain D, et al. H4(D10S170), a gene frequently rearranged in papillary thyroid carcinoma, is fused to the platelet-derived growth factor receptor beta gene in atypical chronic myeloid leukemia with t(5;10)(q33;q22). *Blood*. 2001;97:3910-3918.
 22. Magnusson MK, Meade KE, Brown KE, et al. Rabaptin-5 is a novel fusion partner to platelet-derived growth factor beta receptor in chronic myelomonocytic leukemia. *Blood*. 2001;98:2518-2525.
 23. Wilkinson K, Velloso ER, Lopes LF, et al. Cloning of the t(1;5)(q23;q33) in a myeloproliferative disorder associated with eosinophilia: involvement of PDGFR β and response to imatinib. *Blood*. 2003;102:4187-4190.
 24. Vizmanos JL, Novo FJ, Roman JR, et al. NIN, a gene encoding a CEP110-like centrosomal protein, is fused to PDGFR β in a patient with a t(5;14)(q33;q24) and an imatinib-responsive myeloproliferative disorder. *Cancer Res*. 2004;64:2673-2676.
 25. Morerio C, Acquila M, Rosanda C, et al. HCMOGT-1 is a novel fusion partner to PDGFR β in juvenile myelomonocytic leukemia with t(5;17)(q33;p11.2). *Cancer Res*. 2004;64:2649-2651.
 26. Levine R, Wadleigh M, Sternberg DW, et al. KIAA1509 is a novel PDGFR β fusion partner in imatinib-responsive myeloproliferative disease associated with a t(5;14)(q33;q32). *Leukemia*. In press.
 27. Le Beau MM, Larson RA, Bitter MA, et al. Association of an inversion of chromosome 16 with abnormal marrow eosinophils in acute myelomonocytic leukemia. A unique cytogenetic-clinicopathological association. *N Engl J Med*. 1983;309:630-636.
 28. Swirsky DM, Li YS, Matthews JG, Flemans RJ, Rees JK, Hayhoe FG. 8;21 translocation in acute granulocytic leukaemia: cytological, cytochemical and clinical features. *Br J Haematol*. 1984;56:199-213.
 29. La Starza R, Trubia M, Testoni N, et al. Clonal eosinophils are a morphologic hallmark of ETV6/ABL1 positive acute myeloid leukemia. *Haematologica*. 2002;87:789-794.
 30. Song HS, Park SK. A case of monosomy-7 eosinophilic leukemia and neurofibromatosis, terminated with disseminated cryptococcosis. *Korean J Intern Med*. 1987;2:131-134.
 31. Harrington DS, Peterson C, Ness M, Sanger W, Smith DM, Vaughan W. Acute myelogenous leukemia with eosinophilic differentiation and trisomy-1. *Am J Clin Pathol*. 1988;90:464-469.
 32. Brouster A, Bernard P, Dachary D, et al. Acute eosinophilic leukemia with a translocation (10p+;11q-). *Cancer Genet Cytogenet*. 1986;21:327-333.
 33. Bhabhani K, Inoue S, Tyrkus M, Gohle N. Acute myelomonocytic leukemia type M4 with bone marrow eosinophilia and t(5;16)(q33;q22). *Cancer Genet Cytogenet*. 1986;20:187-188.
 34. Mecucci C, Bosly A, Michaux JL, Broekaert-Van Orshoven A, Van den Berghe H. Acute nonlymphoblastic leukemia with bone marrow eosinophilia and structural anomaly of chromosome 16. *Cancer Genet Cytogenet*. 1985;17:359-363.
 35. Matsushima T, Murakami H, Kim K, et al. Steroid-responsive pulmonary disorders associated with myelodysplastic syndromes with der(1q;7p) chromosomal abnormality. *Am J Hematol*. 1995;50:110-115.
 36. Inhorn RC, Aster JC, Roach SA, et al. A syndrome of lymphoblastic lymphoma, eosinophilia, and myeloid hyperplasia/malignancy associated with t(8;13)(p11;q11): description of a distinctive clinicopathologic entity. *Blood*. 1995;85:1881-1887.
 37. Xiao S, Nalabolu SR, Aster JC, et al. FGFR1 is fused with a novel zinc-finger gene, ZNF198, in the t(8;13) leukaemia/lymphoma syndrome. *Nat Genet*. 1998;18:84-87.
 38. Roumiantsev S, Krause DS, Neumann CA, et al. Distinct stem cell myeloproliferative/T lymphoma syndromes induced by ZNF198-FGFR1 and BCR-FGFR1 fusion genes from 8p11 translocations. *Cancer Cell*. 2004;5:287-298.
 39. Chen J, Deangelo DJ, Kutok JL, et al. PKC412 inhibits the zinc finger 198-fibroblast growth factor receptor 1 fusion tyrosine kinase and is active in treatment of stem cell myeloproliferative disorder. *Proc Natl Acad Sci U S A*. 2004;101:14479-14484.
 40. Cools J, DeAngelo DJ, Gotlib J, et al. A tyrosine kinase created by fusion of the PDGFRA and FIP1L1 genes as a therapeutic target of imatinib in idiopathic hypereosinophilic syndrome. *N Engl J Med*. 2003;348:1201-1214.
 41. Gleich GJ, Leiferman KM, Pardanani A, Tefferi A, Butterfield JH. Treatment of hypereosinophilic syndrome with imatinib mesilate. *Lancet*. 2002;359:1577-1578.
 42. Cortes J, Ault P, Koller C, et al. Efficacy of imatinib mesylate in the treatment of idiopathic hypereosinophilic syndrome. *Blood*. 2003;101:4714-4716.
 43. Pardanani A, Reeder T, Porrata LF, et al. Imatinib therapy for hypereosinophilic syndrome and other eosinophilic disorders. *Blood*. 2003;101:3391-3397.
 44. Weller PF, Bublely GJ. The idiopathic hypereosinophilic syndrome. *Blood*. 1994;83:2759-2779.