Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL AT INIST-CNRS

Leukaemia Section

Mini Review

t(4;22)(q12;q11.2)

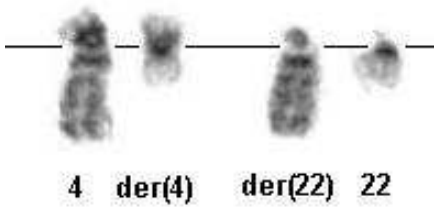
Barbara K Goodman, Anne Michele Safely

Clinical Cytogenetics, Molecular Diagnostics Laboratories, Duke University Health System, Box 3631, Durham, NC 27710, UK (BKG, AMS)

Published in Atlas Database: September 2004

Online updated version : http://AtlasGeneticsOncology.org/Anomalies/t0422q12q11ID1153.html
DOI: 10.4267/2042/38134

Identity



Partial karyotype showing chromosomes 4 and 22.

Clinics and pathology

Disease

Reported in 3 cases; myeloproliferative disorder : atypical chronic myeloid leukemia (aCML) (Philadelphia chromosome-negative).

Etiology

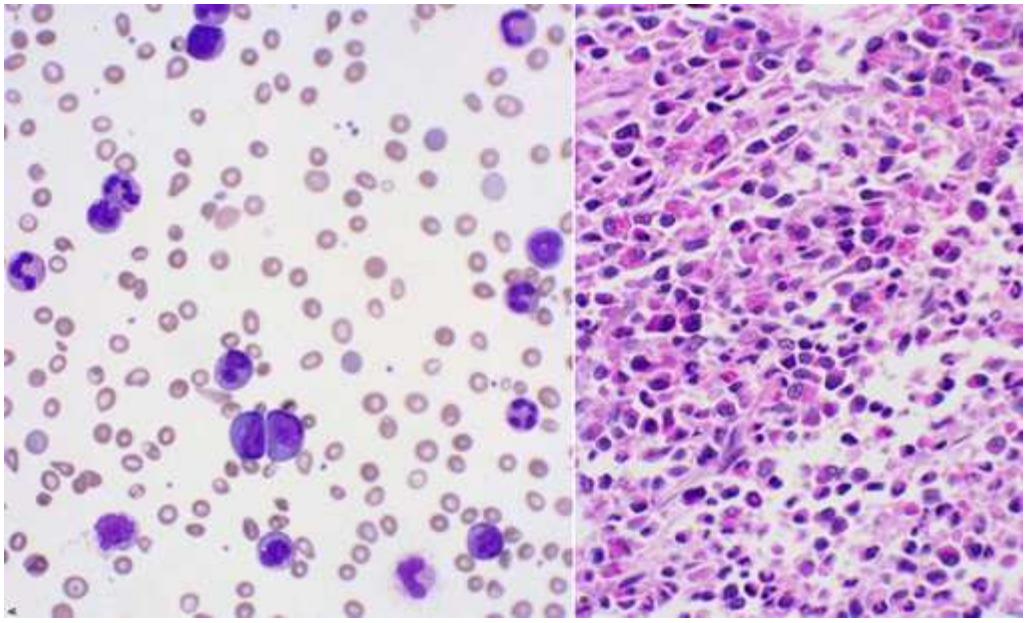
One case was post-treatment for lymphoma, thus suspected to be a secondary MPD.

Clinics

3 cases shared characteristics of splenic enlargement, eosinophilia and male predominance.

Prognosis

One patient on treatment with good response to imatinib mesylate.



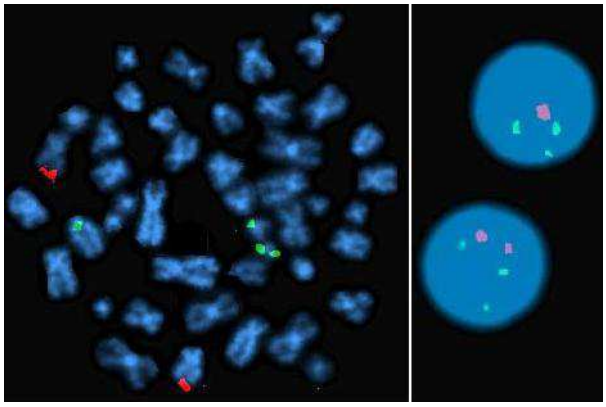
Peripheral blood smear showing anemia, leukocytosis with increased granulocytes and precursors, and eosinophilia. Bone marrow showing hypercellularity with marked myeloid hyperplasia, mild eosinophilia, no increase in blasts.

Cytogenetics

Note
t(4;22)(q12;q11.2), easily distinguished cytogenetically.

Cytogenetics molecular

FISH for BCR- ABL1 is negative for fusion but will show extra signal for BCR when using the dual fusion probe set. BCR-ABL1 PCR is negative.



Interphase FISH showing 3 signals for BCR (green), suggesting rearrangement. Two normal signals for ABL1 (red).

Probes

BCR-ABL dual fusion probe set.

Additional anomalies

The t(4;22) was observed as the sole anomaly in the few reported cases to date.

Genes involved and proteins

PDGFRA

Location
4q12
Note
Member of the protein-tyrosine kinase receptor family subclass III that includes the colony stimulating factor-1, c-KIT, FLT1, and FLT3/FLK2. Suggested role for normal PDGFRA receptor expression during periods of glial cell development and connective tissue growth.
DNA/RNA
23 exons; includes 2 intracellular tyrosine kinase domains, TK1 and TK2 (exons 13-15 and 17-21), 5 extracellular Ig-like domains (exons 3-10), and a hydrophobic transmembrane domain (exon 10). The cytoplasmic region also encodes an ATP binding site.
Protein
170-kD transmembrane glycoprotein that normally binds all PDGF isoforms, AA, AB, and BB at its extracellular Ig domain.

BCR

Location
22q11.2
DNA/RNA
23 exons; alternate splicing.
Protein
160-kDa protein; contains a unique serine/threonine kinase activity and at least two SH2 binding sites encoded in its first exon and a C-terminal domain that functions as a GTPase activating protein for p21(rac).

Result of the chromosomal anomaly

Hybrid gene

Note
5'BCR-3'PDGFRA fusion.
Description
Fusion of BCR exon 7, 12 or 17 (in 3 cases described) with PDGFRA exon 12, in frame, containing intronic sequence from BCR in two cases.

Fusion protein

Description
169 kDa protein in one case, somewhat smaller in two others.
Expression / Localisation
Predicted to be localized intracellularly.
Oncogenesis
Alteration of tyrosine kinase activity secondary to loss of regulatory and PDGF binding domains; also, BCR domains may significantly affect BCR-PDGFRA downstream signaling pathways as seen with BCR-ABL fusion.

References

Claesson-Welsh L, Hammacher A, Westermark B, Heldin CH, Nistér M. Identification and structural analysis of the A type receptor for platelet-derived growth factor. Similarities with the B type receptor. J Biol Chem. 1989 Jan 25;264(3):1742-7

Kawagishi J, Kumabe T, Yoshimoto T, Yamamoto T. Structure, organization, and transcription units of the human alpha-platelet-derived growth factor receptor gene, PDGFRA. Genomics. 1995 Nov 20;30(2):224-32

Lokker NA, O'Hare JP, Barsoumian A, Tomlinson JE, Ramakrishnan V, Fretto LJ, Giese NA. Functional importance of platelet-derived growth factor (PDGF) receptor extracellular immunoglobulin-like domains. Identification of PDGF binding site and neutralizing monoclonal antibodies. J Biol Chem. 1997 Dec 26;272(52):33037-44

Reddy KS, Sulcova V. A FISH study of variant Philadelphia rearrangements. Cancer Genet Cytogenet. 2000 Apr 15;118(2):121-31

Baxter EJ, Hochhaus A, Bolufer P, Reiter A, Fernandez JM, Senent L, Cervera J, Moscardo F, Sanz MA, Cross NC. The t(4;22)(q12;q11) in atypical chronic myeloid leukaemia fuses BCR to PDGFRA. Hum Mol Genet. 2002 Jun 1;11(12):1391-7

Bolaños-Meade J, Sarkodee-Adoo C, Khanwani SL. CML after treatment for lymphoid malignancy: Therapy-related CML or coincidence? Am J Hematol. 2002 Oct;71(2):139

Baxter EJ, Kulkarni S, Vizmanos JL, Jaju R, Martinelli G, Testoni N, Hughes G, Salamanchuk Z, Calasanz MJ, Lahortiga I, Pocock CF, Dang R, Fidler C, Wainscoat JS, Boultwood J, Cross NC. Novel translocations that disrupt the platelet-derived growth factor receptor beta (PDGFRB) gene in BCR-ABL-negative chronic myeloproliferative disorders. Br J Haematol. 2003 Jan;120(2):251-6

Heinrich MC, Corless CL, Duensing A, McGreevey L, Chen CJ, Joseph N, Singer S, Griffith DJ, Haley A, Town A, Demetri GD, Fletcher CD, Fletcher JA. PDGFRA activating mutations in gastrointestinal stromal tumors. Science. 2003 Jan 31;299(5607):708-10

Trempat P, Villalva C, Laurent G, Armstrong F, Delsol G, Dastugue N, Brousset P. Chronic myeloproliferative disorders with rearrangement of the platelet-derived growth factor alpha receptor: a new clinical target for STI571/Glivec. Oncogene. 2003 Aug 28;22(36):5702-6

Safley AM, Sebastian S, Collins TS, Tirado CA, Stenzel TT, Gong JZ, Goodman BK. Molecular and cytogenetic characterization of a novel translocation t(4;22) involving the breakpoint cluster region and platelet-derived growth factor receptor-alpha genes in a patient with atypical chronic myeloid leukemia. Genes Chromosomes Cancer. 2004 May;40(1):44-50

This article should be referenced as such:

Goodman BK, Safely AM. t(4;22)(q12;q11.2). Atlas Genet Cytogenet Oncol Haematol. 2004; 8(4):328-330.