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Leukaemia Section
Short Communication

t(5;6)(q33-34;q23) CEP85L/PDGFRB

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Clinics and pathology

Disease

Precursor T-cell lymphoblastic lymphoma (T-ALL) with an association myeloproliferative neoplasm (MPN) with eosinophilia.

Epidemiology

Very rare; 1 case reported (Chmielecki et al., 2011).

Clinics

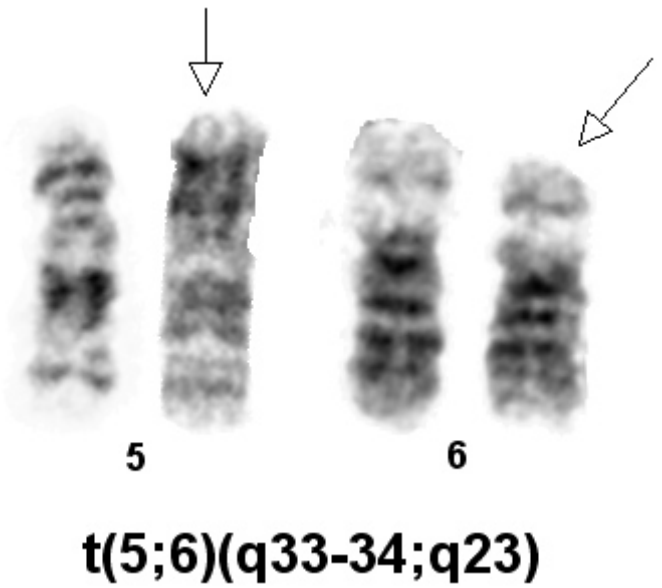
The patient was a 38 year-old male with a history of precursor T lymphoblastic lymphoma, a myeloid neoplasm associated neoplasm associated with eosinophilia, and a t(5;6)(q33-34;q23) identified by metaphase cytogenetics.

Treatment

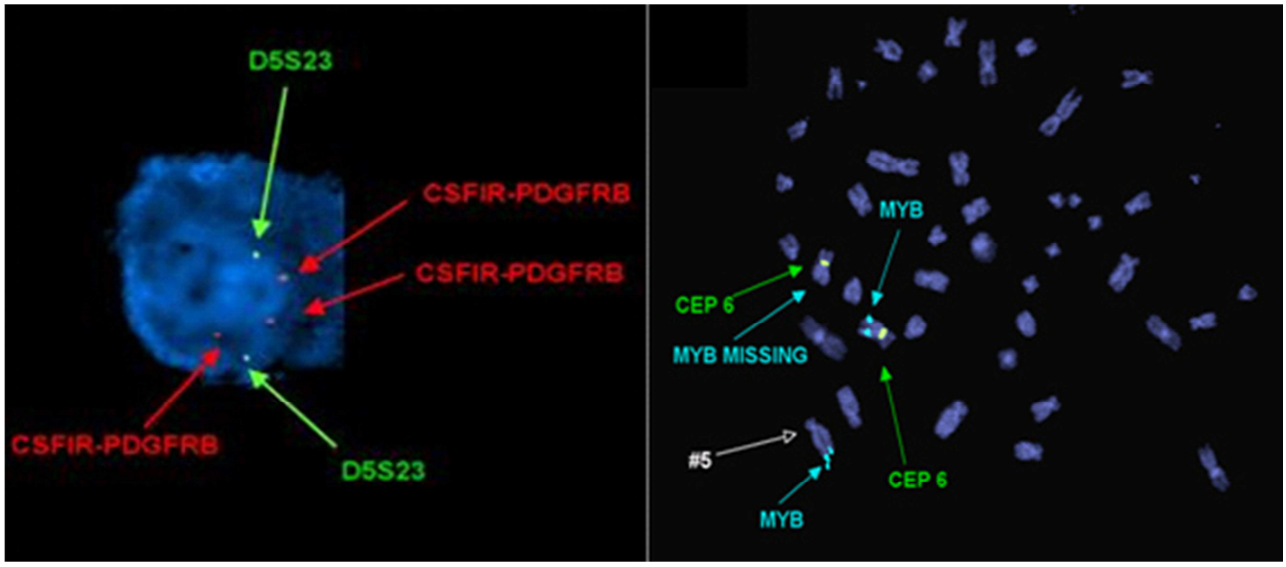
The patient received a brief 5-day course of imatinib therapy, prior to allogenic stem cell transplantation, which resulted in resolution of his eosinophilia (white blood cell counts decreased from 27.3 to 5.4 thou/µL; normal range (3.9-10.7 thou/µL).

Prognosis

In patients with myeloid neoplasms associated with eosinophilia, imatinib is also highly active against TK fusions involving PDGFRA and PDGFRB (David et al., 2007; Vardiman et al., 2009).



Karyotype analysis of the bone marrow showed a translocation involving chromosomes 5 and 6: t(5;6)(q33-34;q23).



Fluorescence in situ hybridization (FISH) of a lymph node shows one split red signal (CSF1R-PDGFRB), one normal red signal, and two normal green signals (D5S23), suggesting existence of a rearrangement involving PDGFRB (LEFT). FISH analysis with a probe against MYB on chromosome 6 (marked by CEP 6 probe) shows one copy of MYB is now located on chromosome 5, suggesting involvement of MYB in the translocation (RIGHT).

Genetics

Note

The c6orf204-PDGFRB fusion protein fuses exon 11 of CEP85L/C6orf204 to exon 12 of PDGFRB.

The cDNA breakpoint within PDGFRB is the same as that observed in the NIN-PDGFRB fusion, previously observed in another case of an imatinib-responsive myeloproliferative neoplasm (Vizmanos et al., 2004).

The break within PDGFRB occurs just downstream of the transmembrane domain, removing the five immunoglobulin-like domains found within the extracellular domain but leaving the tyrosine kinase domain intact.

The 5' sequence observed in our fusion protein could have resulted from two isoforms (a and c) arising from alternative transcriptional start sites and differing only in the first 24 amino acids. RT-PCR analysis using an anchored reverse primer and forward primers specific to isoforms a or c confirmed that the 5' sequence of the fusion originated from the isoform c start site. Motif analysis of C6orf204 revealed the presence of a coiled-coil domain just N-terminal to the breakpoint observed in the C6orf204-PDGFRB fusion. The presence of a coiled-coil domain-containing 5' partner is a common occurrence in tyrosine kinase fusions involving PDGFRB and other tyrosine kianses (Vizmanos et al., 2004), as it facilitates dimerization necessary for kinase (Carroll et al., 1996; Grisolano et al., 2003; Vizmanos et al., 2004; Taylor and Keating, 2005). The fusion here removes the last 8 amino acids of the domain. In vitro, a C6orf204-PDGFRB fusion product, generated via transient transfection of 293T cells with an expression plasmid, showed increased PDGFRB phosphorylation relative to mock transfected cells; such phosphorylation was inhibited by imatinib.

Combined with the clinical response data, these studies indicate that the C6orf204-PDGFRB fusion is likely the 'driver' of the patient's eosinophilia.

Cytogenetics

Cytogenetics molecular

FISH analysis of the patient's lymph node suggested a rearrangement involving PDGFRB.

Probes

FISH was performed using standard procedures with CSF1R-PDGFRB (5q31-33 region) spectrum orange, D5S23 and D5S721 (5p15.2 region) spectrum green, and MYB (6q23) spectrum aqua unique sequence DNA probes and a chromosome 6 (D6Z1) spectrum green centromere probe (Abbott Molecular, Downers Grove, IL).

Additional anomalies

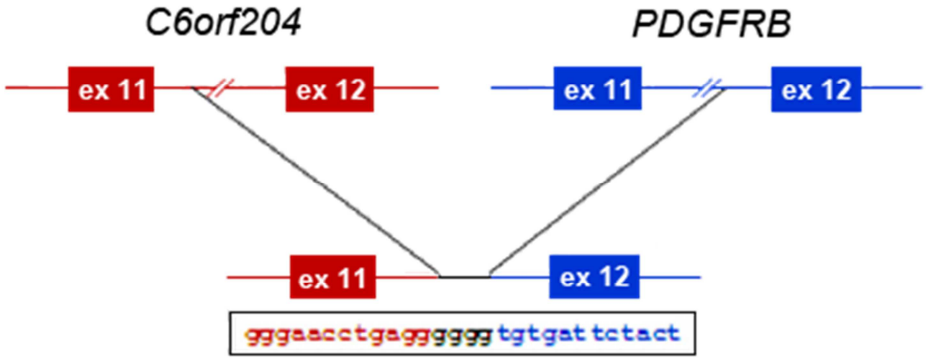
FISH analysis of the patient's diagnostic lymph node with T-ALL also revealed the presence of a PDGFRB rearrangement, suggesting that this event occurred in a common clonal precursor that gave rise to both the T-ALL and eosinophilia.

Genes involved and proteins

PDGFRB

Location

5q32



Genomic structure of the in-frame c6orf204-PDGFRB fusion.

DNA/RNA
23 exons.

Protein
Platelet-derived growth factor receptor beta (PDGFRb) is a catalytic receptor with intrinsic intracellular tyrosine kinase activity. It plays a role in the regulation of many biological processes including embryonic development, angiogenesis, cell proliferation and differentiation, and contribute to the pathophysiology of some diseases, including cancer (adapted from GeneCards).

CEP85L

Location
6q22.31

Note
The 5' sequence observed in our fusion protein could have resulted from two isoforms (a and c) arising from alternative transcriptional start sites and differing only in the first 24 amino acids.

DNA/RNA
13-14 exons (depending on isoform).

Protein
The gene encoding CEP85L/c6orf204 was originally identified as a breast cancer antigen (Scanlan et al., 2001).

Result of the chromosomal anomaly

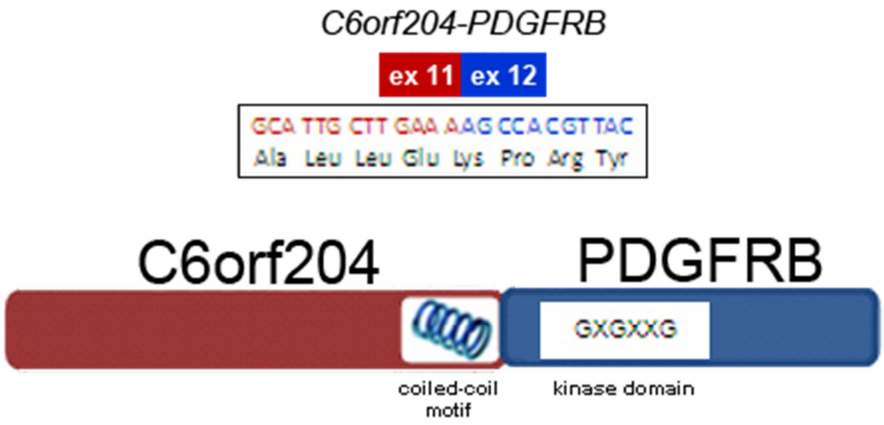
Hybrid gene

Description
Exons 1-11 of c6orf204 fuse to exons 12-23 of PDGFRB.

Fusion protein

Description
Amino acids 1-677 of c6orf204 (isoform c) fused to amino acids 559-1106 of PDGFRB.

Oncogenesis
The patient's clinical response to imatinib therapy suggests that this fusion is the "driver" oncogene behind the eosinophilia.



cDNA structure of the in-frame c6orf204-PDGFRB fusion. The resultant protein sequence is indicated below the cDNA sequence (TOP). Schematic showing the entire structure of the c6orf204-PDGFRB fusion protein including the coiled-coil domain within c6orf204 and the tyrosine kinase domain within PDGFRB.

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