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Leukaemia Section

Review

Myeloid/Lymphoid neoplasms with abnormalities of PDGFRB

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Abstract

This insert represents a review of myeloid and lymphoid neoplasms with abnormalities of PDGFRB including clinical presentation, morphologic review, and cytogenetic findings.

KEYWORDS

Myeloid and lymphoid neoplasms with abnormalities of PDGFRB; PDGFRB; eosinophilia; chronic myelomonocytic leukemia; tyrosine kinase inhibitor

Clinics and pathology

Disease

Myeloid and lymphoid neoplasms with abnormalities of PDGFRB are neoplasms in which eosinophilia is typical, although not required. Gene fusions with PDGFRB were first described by Golub et al. in 1994 in a patient with features consistent with chronic myelomonocytic leukemia (CMML). Since that time, over 20 fusion partners have been described. The entity was first formally accepted in the 2008 edition of the World Health Organization's Classification of Tumours of Haematopoietic and Lymphoid Tissues along with abnormalities of PDGFRA and FGFR1. In the WHO 2016 edition, myeloid and lymphoid neoplasms with eosinophilia and t(8;9)(p22;p24.1) PCM1 / JAK2 is now recognized as a provisional entity.

Phenotype/cell stem origin

The cell of origin is a hematopoietic cell with commitment to eosinophilic differentiation.

Epidemiology

Myeloid and lymphoid neoplasms with eosinophilia and abnormalities of PDGFRB (as well as abnormalities of PDGFRA and FGFR1) are rare. Adult males are most commonly affected with a median age of onset in the late forties; however, older adults and rarely children have also been affected.

Clinics

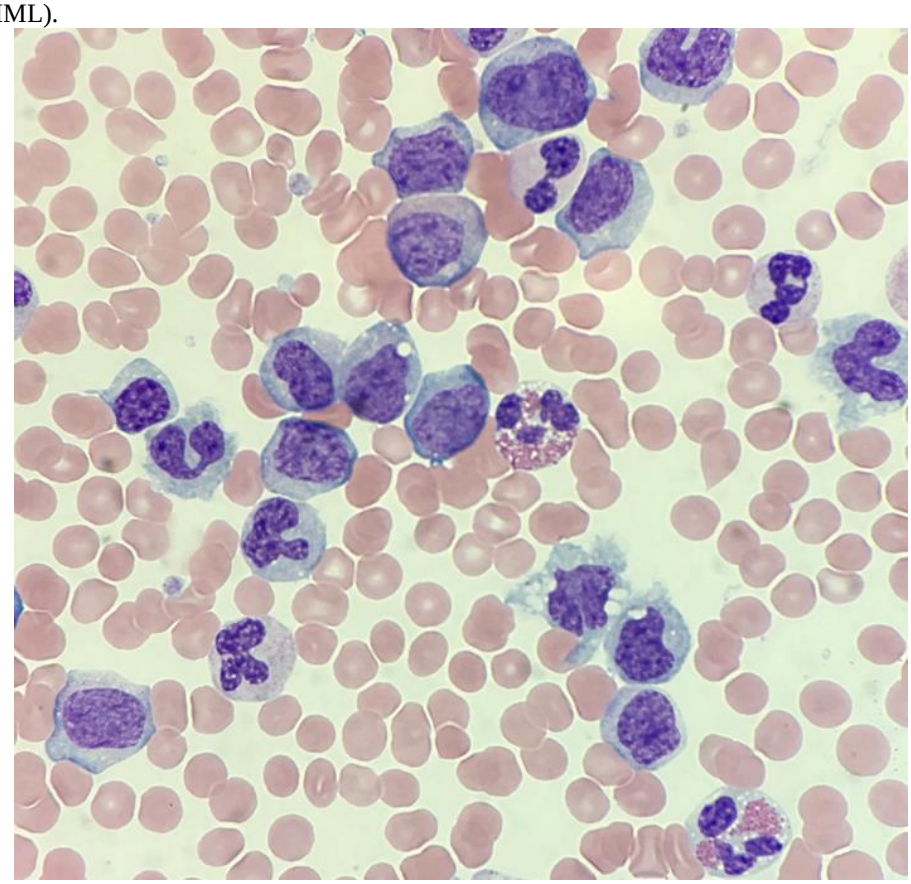
Patients typically present with splenomegaly with hepatomegaly being less frequent; lymphadenopathy may also be seen. As with abnormalities of PDGFRA, skin and cardiac infiltration may be present at diagnosis with resulting cardiac damage.

Pathology

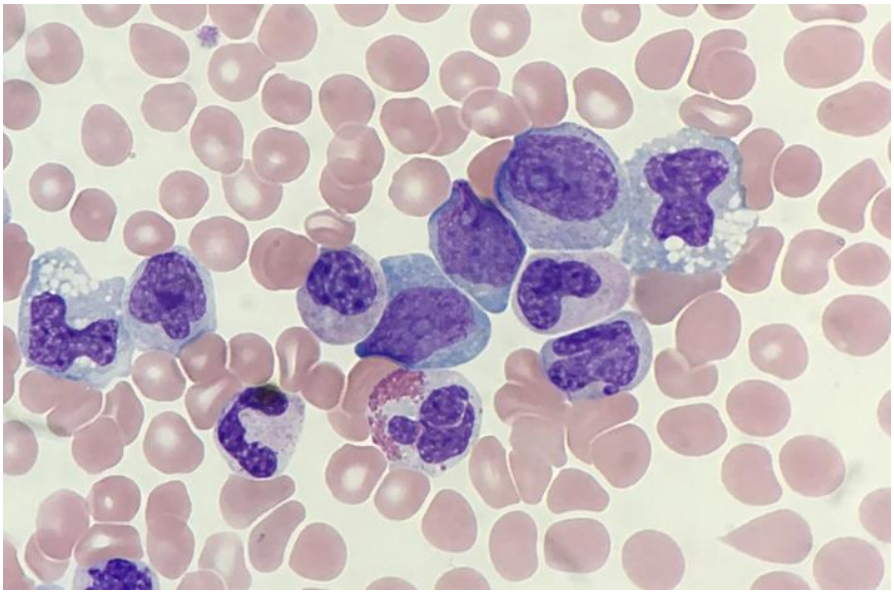
In patients with abnormalities of PDGFRB, peripheral blood and bone marrow are almost always involved with typical leukocytosis and possible concordant anemia and/or thrombocytopenia. Leukocytosis is usually predominated by monocytosis and eosinophilia imparting a chronic myelomonocytic leukemia (CMML)-like picture with eosinophilia (Figure 1 and 2). Eosinophils may have atypical morphology. Rarely, basophilia is also prominent. However, some patients present with

features more suggestive of atypical chronic myeloid leukemia without BCR / ABL1 (aCML) or chronic eosinophilic leukemia (CEL) or more rarely, they present with phenotypic features of acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), or juvenile myelomonocytic leukemia (JMML).

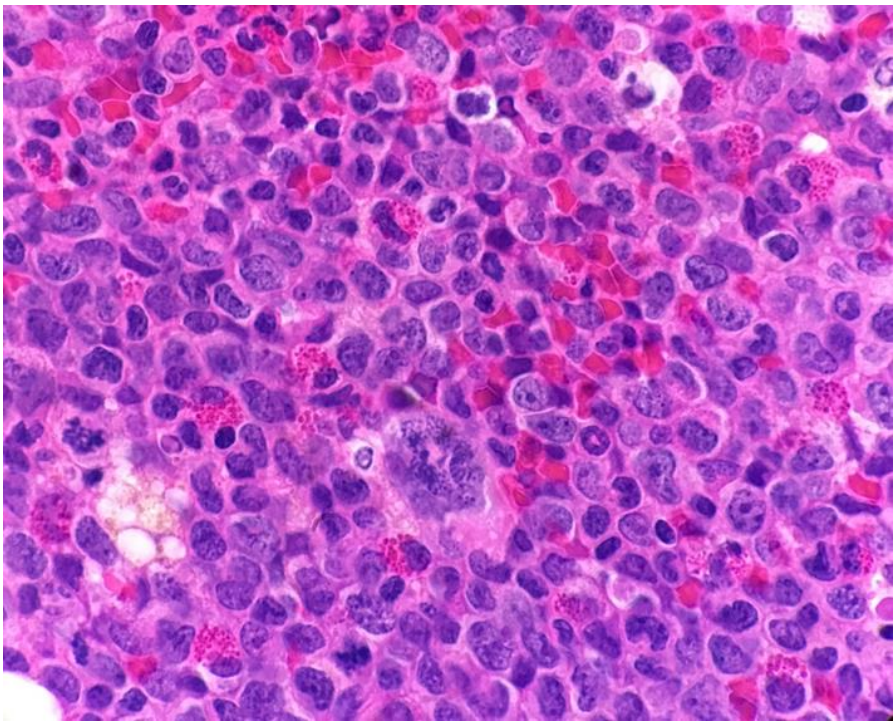
The bone marrow is typically hypercellular (Figure 3) with accompanying fibrosis. As in cases with PDGFRA abnormalities, mast cell aggregates (not meeting criteria for systemic mastocytosis) can be seen.



Monocytosis is seen along with atypical eosinophils with cytoplasmic vacuolation, uneven granule distribution, and increased nuclear lobes. (Wright Giemsa stained peripheral blood smear, original magnification 500x)



Leukocytosis is noted with increased monocytes and several blasts. In addition, an atypical eosinophil is noted with sparse uneven granule distribution. (Wright Giemsa stained peripheral blood smear, original magnification 1000x)



A markedly hypercellular bone marrow with myeloid hyperplasia including many eosinophils is appreciated. (Hematoxylin and Eosin stained bone marrow biopsy, original magnification 500x)

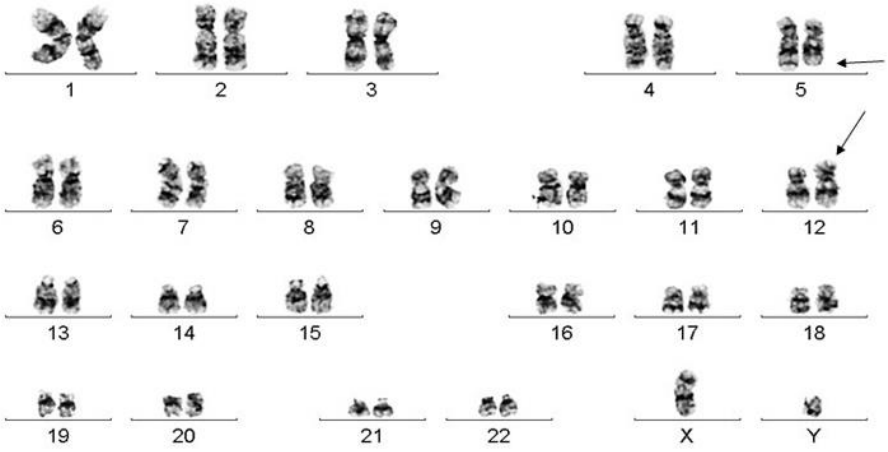
Treatment

Patients with abnormalities of PDGFRB are exquisitely sensitive to imatinib, like patients with abnormalities of PDGFRA, and this is the drug if choice. Primary and secondary resistance is uncommon; initial response typically occurs within 2 months.

Prognosis

Previously, this neoplasm was cited as an aggressive disease with a median overall survival of less than 2 years. However, after the universal initiation of imatinib as standard therapy, a recent study cited a 10-year overall survival of 90% (Cheah et al., 2014).

Cytogenetics



G-banded karyotype demonstrating 46,XY,t(5;12)(q33.1;p13.2).

Cytogenetics morphological

PDGFRB can have a variety of fusion partners with more than 20 currently described (Table 1), but by far the most common fusion is ETV6-PDGFRB. Conventional karyotyping usually readily identifies 5q33 (PDGFRB) rearrangements (Figure 4). Multicolor FISH has also been useful in recognizing PDGFRB rearrangements or confirming suspected fusion on karyotype by using probes that closely flank both ends of the gene.

Fusion partner genes and locations

ETV6	12p12
CCDC88C	14q32
CCDC6	10q21
TRIP11	14q32
TPM3	1q21
CAPRIN1	1p11
GIT2	12q24
RABEP1	17p13
CEP85L	6q22
PRKG2	4q21
COL1A1	17q21
NDE1	16p13
SPTBN1	2p21
PDE4DIP	1q21
TP53BP1	15q15-q21
SPECC1	17p11
GOLGA4	3p22
HIP1	7q11
BIN2	12q13
MYO18A	17q11
NIN	14q22
SART3	12q23
ERC1	12p13
WDR48	3p21
DTD1	20p11
KANK1	9p24

Genes involved and proteins

PDGFRB (platelet-derived growth factor receptor, beta polypeptide)

Location

5q32

Note

Platelet Derived Growth Factor Receptor Beta (PDGFRB) is located on chromosome 5, band q32. It contains 23 exons and spans approximately 149.5 Mb. The encoded protein is 1067 amino acids. As with PDGFRA, it is a member of the type III class of tyrosine kinase receptors.

Result of the chromosomal anomaly

Hybrid gene

Note

The most common fusion gene produced is the ETV6 /PDGFRB, due to t(5;12)(q31~33;p13), which is typically detected via conventional karyotyping. However, many fusion partners are described as PDGFRB is known to be the most promiscuous of all of the genes involved in myeloid and lymphoid neoplasms with eosinophilia (and abnormalities of PDGFRA, PDGFRB, or FGFR1). This fusion gene produces an activated tyrosine kinase that transforms hematopoietic cells due to constitutive activation.

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