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Leukaemia Section

Review

Myeloid/Lymphoid neoplasms with abnormalities of PDGFRA

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Abstract

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

KEYWORDS
Myeloid and lymphoid neoplasms with abnormalities of PDGFRA; PDGFRA; CHIC2; eosinophilia; chronic eosinophilic leukemia; tyrosine kinase inhibitor

Identity

Myeloid/Lymphoid neoplasms with abnormalities of PDGFRA

Clinics and pathology

Disease

Myeloid and lymphoid neoplasms with abnormalities of PDGFRA are neoplasms in which eosinophilia is highly typical, although not required. For years, most patients with eosinophilia and abnormalities of PDGFRA were diagnosed with hypereosinophilic syndrome (HES) as karyotype was frequently normal and no secondary cause was identified. However, in 2001, a subset of patients with HES were found to show responsiveness to tyrosine kinase inhibitors (TKI), specifically imatinib. Investigation of the tyrosine kinases within these patients revealed a cryptic deletion resulting in fusion of PDGFRA to FIP1L1. After this groundbreaking research, 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 PDGFRB 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. These clonal eosinophils may show evidence of activation by immunohistochemistry, with CD23, CD25, and/or CD69 expression.

Epidemiology

There is an overwhelming male predominance with a median age of onset of 40-years-of age, although they may present across a broad age range.

Clinics

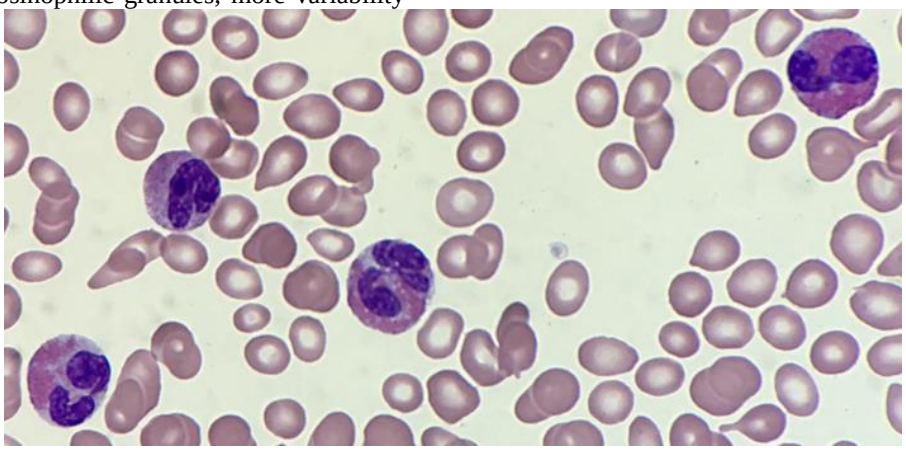
Patients with hematopoietic neoplasms involving PDGFRA often present with fatigue or pruritic rash.

Multi-organ tissue damage, including respiratory, gastrointestinal, or cardiac sequelae, is well reported due to tissue infiltration by clonal eosinophils. Physical examination reveals splenomegaly in most patients and hepatomegaly within a minority. Peripheral blood smear traditionally shows features suggestive of chronic eosinophilic leukemia (CEL). Although abnormalities of PDGFRA usually resemble CEL, rarely, patients may display characteristics of acute myeloid leukemia (AML) or T-cell lymphoblastic leukemia/lymphoma (T-ALL/LBL). However, eosinophilia traditionally remains a consistent feature.

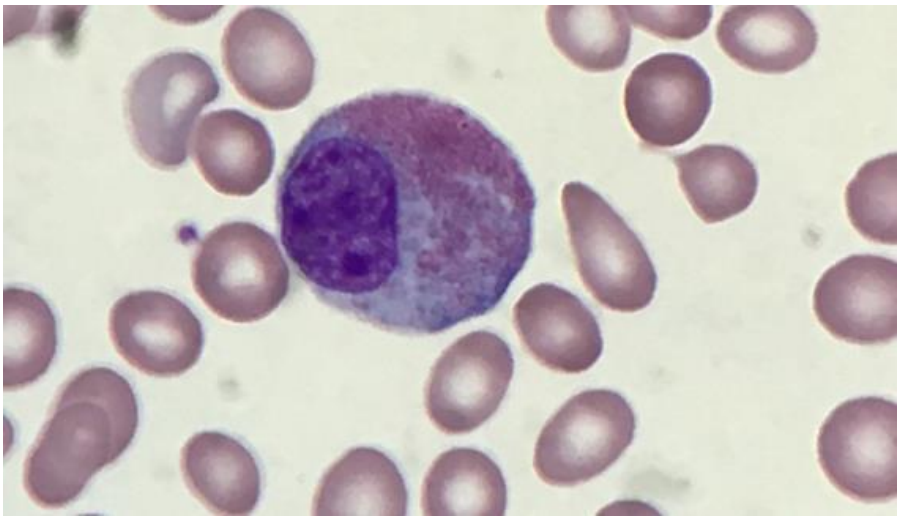
Pathology

In patients with abnormalities of PDGFRA, eosinophilic atypia may be present (Figure 1), but is variable and not required. This includes atypical nuclear segmentation, hypogranular cytoplasm with puddling of eosinophilic granules, more variability in granule texture/color, and cytoplasmic vacuolation. Eosinophils are typically mature with usually only rare eosinophilic precursors noted (Figure 2). Anemia and thrombocytopenia are common, while monocytosis and basophilia are infrequent (Savage et al., 2013).

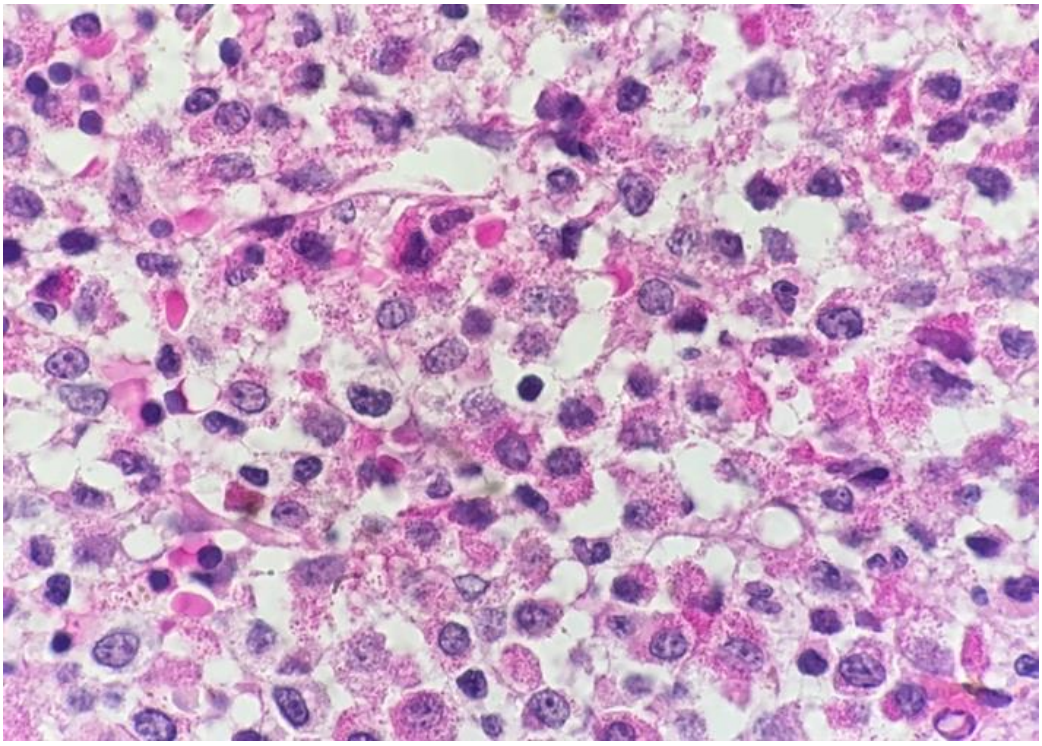
Bone marrow trephine biopsies are typically hypercellular with increased eosinophils and their precursors (Figure 3) (Bain et al., 2008). Fibrosis may also be increased and can be highlighted with a reticulin histochemical stain (Figure 4). Mast cells are often increased as well, either in loose or cohesive clusters, and may have atypical spindled morphology. Moreover, they may have an aberrant immunophenotype, frequently expressing CD25 or even CD2 and CD25. However, the findings usually fall short of criteria for systemic mastocytosis as KIT D816V mutation is not present and serum tryptase levels are typically less than 20 ng/mL.



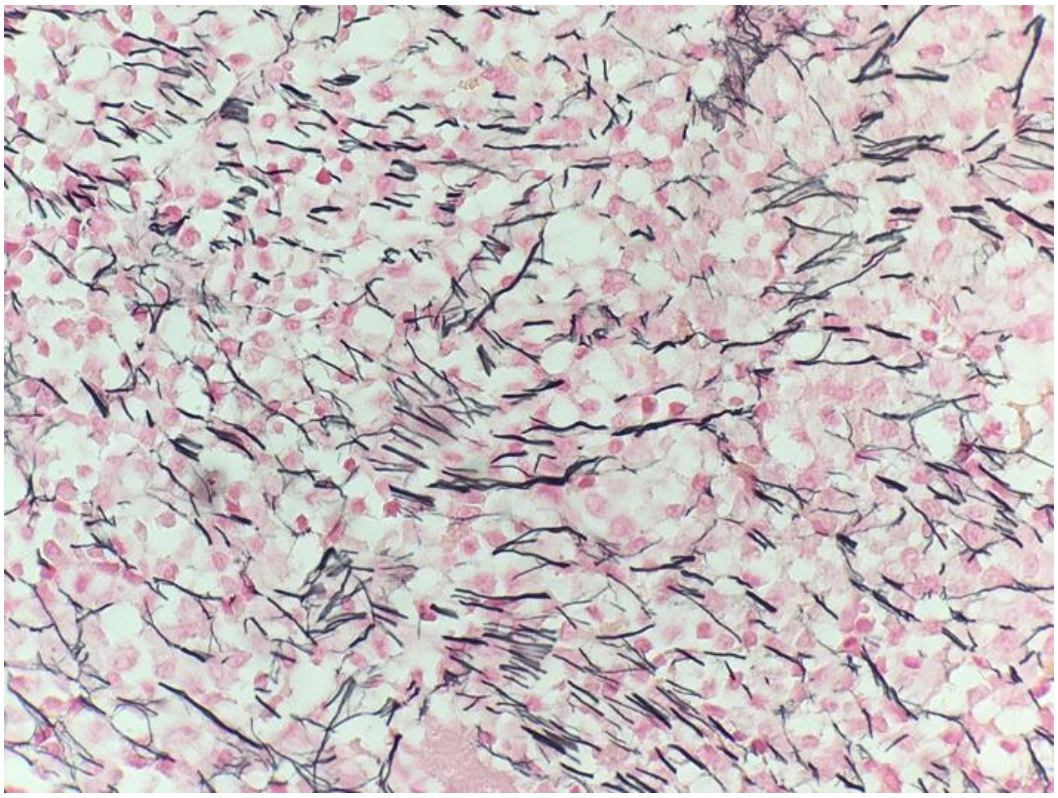
In this smear obtained from a patient with PDGFRA abnormality, eosinophilia is noted with some atypical morphology. Specifically, granules unevenly fill the cytoplasm with one eosinophil having few cytoplasmic vacuoles. In addition, the nuclear segmentation is atypical with increased nuclear lobes noted in one eosinophil. (Wright Giemsa stained peripheral blood smear, original magnification 500x).



Here an immature eosinophil is noted (eosinophilic myelocyte) with uneven granule distribution; moreover, the granules appear more fine than typical for an eosinophilic precursor. (Wright Giemsa stained peripheral blood smear, original magnification 1000x).



The bone marrow is hypercellular due numerous eosinophilic precursors. (Hematoxylin and Eosin stained bone marrow biopsy, original magnification 500x).



Reticulin histochemical stain highlights increased bone marrow fibrosis. (Reticulin histochemical stain of bone marrow biopsy, original magnification 500x).

Treatment

Patients with abnormalities of PDGFRA are exquisitely sensitive to imatinib. An initial dose of 100 mg per day leads to complete hematologic response in most patients. If imatinib is discontinued secondary to adverse reactions or very rarely due to resistance, it can be replaced by second or third generation TKI.

Prognosis

Prior to identification of this neoplasm with response to TKI, prognosis was poor. However, now while on maintenance therapy, >90% of patients will achieve complete molecular response. Prognosis is excellent particularly if therapy is initiated prior to organ damage especially cardiac sequela.

Cytogenetics

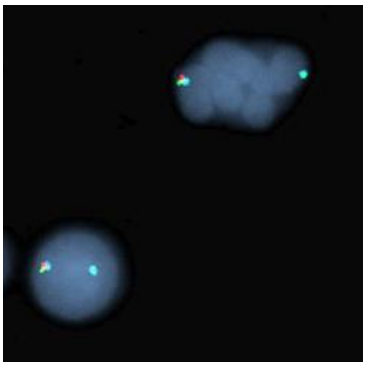
Cytogenetics morphological

Although a number a fusion partners for PDGFRA have been identified (Table 1), the most common by far is FIP1L1 (Bain et al., 2008). The FIP1L1-PDGFRA fusion gene is created by an interstitial deletion on chromosome 4q12 (Cools et al., 2003); this deletion includes cysteine-rich hydrophobic domain 2 (CHIC2) (Pardanani et al., 2003). The deletion is most often cryptic resulting in a normal karyotype, necessitating FISH for identification (Figure 4). However, rarely it may be caused by chromosomal rearrangement. .

Fusion partner genes and locations

FIP1L1	4q12
BCR	22q11
ETV6	12p13
STRN	2p22
CDK5RAP2	9q33
KIF5B	10p11
FOXP1	3p13

Table 1. Myeloid and lymphoid neoplasms with eosinophilia and abnormalities of PDGFRA - reported fusion partners.



FIP1L1 (green), CHIC2 (red), and PDGFRA (aqua) probes reveal nuclei with one intact FIP1L1/CHIC2/PDGFRA signal and one signal with FIP1L1/PDGFRA indicating CHIC2 deletion. (PDGFRA FISH; photo courtesy of Dr. Robert Jenkins of the Mayo Clinic)

Genes involved and proteins

PDGFRA (platelet-derived growth factor receptor, alpha polypeptide)

Location

4q12

Note

Platelet Derived Growth Factor Receptor Alpha (PDGFRA) is located on chromosome 4, band q12. It contains 23 exons and spans approximately 65 kb. The encoded protein is 1089 amino acids with molecular weight of 122670 Da. It is inactive as a monomer in the absence of bound ligand. It is a member of the type III class of tyrosine kinase receptors. It contains 5 immunoglobulin-like extracellular domains, a single transmembrane domain, and an intracellular split kinase domain. The protein plays an essential role in the regulation of many biological processes which include cell proliferation, differentiation, migration, and survival.

Result of the chromosomal anomaly

Hybrid gene

Note

The most common fusion gene produced is the FIP1L1-PDGFRA, which is due to a deletion involving the intervening CHIC2 gene (~800 kb interstitial chromosomal deletion), which is frequently cryptic via conventional karyotyping. This results in an activated tyrosine kinase that transforms hematopoietic cells from constitutive activation of PDGFRA.

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