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Myeloid/Lymphoid Neoplasms with Eosinophilia and Platelet Derived Growth Factor Receptor Alpha (PDGFRA) Rearrangement

Prabhjot Kaur • Wahab A. Khan

Department of Pathology and Laboratory Medicine, Dartmouth-Hitchcock Medical Center, One Medical Center Drive, Lebanon, NH, USA

Author for correspondence: Prabhjot Kaur, Department of Pathology and Laboratory Medicine, Dartmouth-Hitchcock Medical Center, One Medical Center Drive, Lebanon, NH 03756. Email Prabhjot.Kaur@hitchcock.org

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Abstract: Myeloid and lymphoid neoplasms with eosinophilia and *PDGFRA* rearrangements are recognized as a distinct entity within the section of "Myeloid/Lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions (MLN-TK)". Based on the WHO classification of tumors of Hematopoietic and Lymphoid tissues (5th Ed, 2022), these neoplasms also comprise of *PDGFRB* rearrangement, *FGFR1* gene rearrangements, *JAK2* rearrangement, *FLT3* rearrangement, *ETV6*::*ABL1* fusion as well as some others. Of note, these are recently defined entities and are still evolving. In this chapter, practical issues regarding diagnosis, cytogenetic testing, molecular studies, therapeutics, and clinical

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implications are discussed. Differential diagnosis in consideration for eosinophilia and hypereosinophilic syndrome are further highlighted.

Keywords: *CHIC2* deletion; *FIP1L1-PDGFRA* neoplasm; hypereosinophilic syndrome; myeloid/lymphoid neoplasms; *PDGFRA* rearrangement

INTRODUCTION

Myeloid/Lymphoid neoplasms with eosinophilia (M/LN-Eo) harboring gene rearrangements of *PDGFRA*, *PDGFRB, FGFR1*, *JAK2* were first recognized as a separate category of hematolymphoid neoplasms, by the World Health Organization (WHO) in 2008 (1). This entity was further revised in WHO-2016 (2) and WHO-5th Edition (3), as neoplasms within this category shared some features. These include: (i) eosinophilia, (but, not always); (ii) presence of a fusion gene product or a mutation that results in expression of an aberrant tyrosine kinase with therapeutic implications; and (iii) cell origin postulated to be a mutated pluripotent (lymphoid-myeloid) stem cell. Currently, genetic abnormalities defining myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions (MLN-TK) include *PDGFRA* rearrangement, *PDGFRB* rearrangement, *FGFR1* rearrangement, *JAK2* rearrangement, *FLT3* rearrangement, *ETV6::ABL1* fusion and additional tyrosine kinase fusions such as *ETV6::FGFR2*, ETV6::NTRK3; *RANBP2::ALK; BCR::RET; FGFR1OP::RET* (1).

The MLN-TK category of neoplasms usually present as chronic myeloid entities with eosinophilia (usually >1.5 × 10^9/L) such as chronic eosinophilic leukemia (CEL), atypical chronic myeloid leukemia (aCML) or chronic myelomonocytic leukemia (CMML), among others. These neoplasms can rarely present as acute myeloid leukemia (AML) or B/T lymphoblastic leukemia/lymphoma (B/T LBLL). They are negative for the Philadelphia (Ph) chromosome or the presence of a *BCR-ABL1* fusion (2, 4–7). Most of these entities are recognized when they present with eosinophilia, which can prompt molecular cytogenetic interrogation for *PDGFRA*, *PDGFRB*, *FGFR1*or *PCM1-JAK2* abnormalities. Neoplasms that lack eosinophilia have mostly been detected as a serendipitous finding in sequencing studies.

MYELOID/LYMPHOID NEOPLASMS WITH EOSINOPHILIA AND *PDGFRA* REARRANGEMENTS

Myeloid/Lymphoid neoplasms with eosinophilia and *PDGFRA* rearrangements is a rare syndrome with striking male predominance (M: F approximately 16:1 overall). The reported median age is 40 (range 7–77 years) (7–10). The clinical findings include fatigue, pruritus, respiratory, cardiac, or pulmonary symptoms. Pulmonary symptoms include dyspnea and cough with components of both restrictive and obstructive pulmonary disease. Cardiac symptoms may include endomyocardial fibrosis, Loeffler endocarditis and valvular regurgitation. Asymptomatic cases have also been reported (5). Absolute eosinophil counts range from 5.4 to 71.7 × 10^3/µl (median 12.5 × 10^3/µl). The serum tryptase is

elevated (>12 ng/mL) with a range from 6.5–45 ng/mL (median 24 ng/mL). Serum Vit B12 is also increased (8, 11, 12). These neoplasms usually present as CEL with significant involvement of the mast cell lineage and sometimes the neutrophil lineage. Rarely, they present as AML, T-LBLL or with transformation as B-LBLL with accompanying eosinophilia (5). Organ damage occurs as a result of leukemic infiltration or release of cytokines, enzymes or other proteins by eosinophils.

Microscopy

Peripheral blood findings are significant for eosinophilia which are usually mature eosinophils (Figure 1). Rare numbers of eosinophil precursors can be seen. Abnormal morphology with sparse granulation, cytoplasmic vacuolation, abnormal hyper- or hyposegmentation can be seen. These changes are also observed in reactive etiologies and therefore not significantly helpful. There can be neutrophilia, while monocytosis and basophilia are not common. Anemia and thrombocytopenia can be seen. Bone marrow aspirates demonstrate numerous eosinophils and eosinophilic precursors (4, 13–15) (Figure 1). The bone marrow core biopsies are hypercellular with increased eosinophils and precursors. The megakaryocytes demonstrate normal morphology or are myeloproliferative neoplasm-like (MPN-like), myelodysplastic syndrome-like (MDS-like), or mixed MDS/MPN-like. Mast cells are usually increased and present as scattered or loose aggregates.

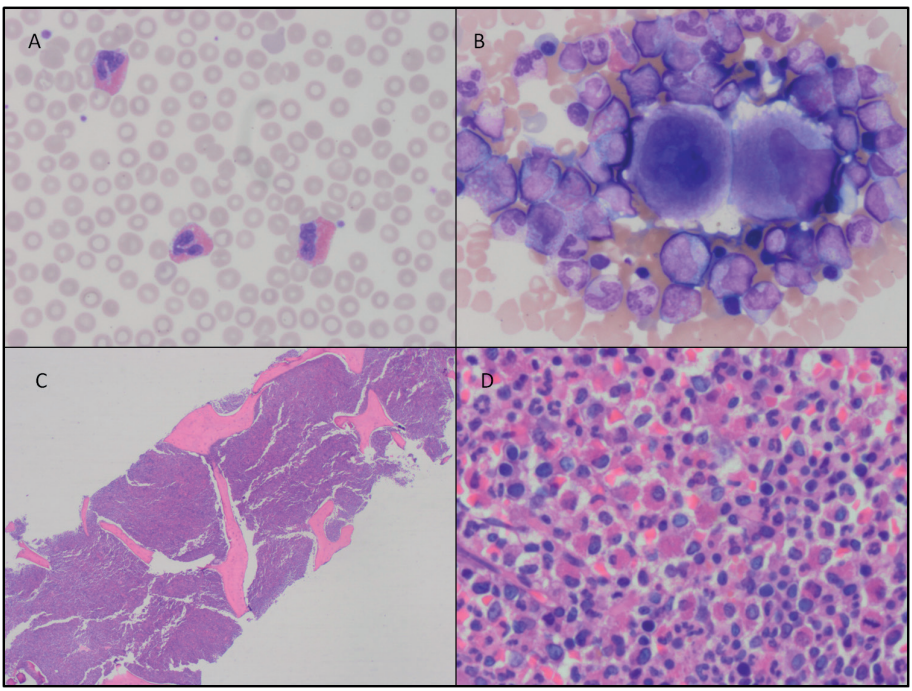

Figure 1. Microscopy. **A.** Peripheral smear with absolute eosinophilia. **B.** Aspirate with increased eosinophils **C, D.** Hypercellular marrow with increased eosinophils.

The dense compact aggregates of spindled mast cells typically associated with systemic mastocytosis appear to be rare in *FIP1L1-PDGFRA* fusion positive cases (9).

They can be seen as atypical spindle shaped mast cells which show aberrant expression of CD2 and/or CD25 and/or CD30 (Figure 2). Mast cell aggregates are usually not typically obvious in routine hematoxylin and eosin-stained sections and are highlighted by immunohistochemical stains for mast cell tryptase or CD117 (C-KIT). Using immunohistochemistry or flow cytometry, the mast cells are shown to be positive for CD117, CD25 +/- and CD2 +/- expression. Bone marrow (BM) fibrosis is also observed in some of these cases. Myeloid sarcoma/extramedullary involvement can be seen in a significant subset (7). The most common extramedullary sites are lymph node, epidural or spinal masses, and rarely cutaneous involvement or oral mass. These usually demonstrate infiltration with maturing myeloid elements and associated eosinophilia containing various degrees of fibrosis. Necrosis can be seen in these extramedullary sites. Immature cells/blasts are seen in myeloid sarcoma, monocytic sarcoma or B/T lymphoblastic lymphoma/leukemia. In cases presenting with T-LBL, B-LBL, or T-cell lymphoma, the diagnosis of the M/LN-Eo with *PDGFRA* rearrangement is suspected either based on the BM findings or have been incidentally discovered by RNA sequencing analysis (7). This illustrates the importance of BM examination and maintaining a low threshold for fluorescence *in situ* hybridization (FISH) or RNA-sequencing testing in the assessment of the extramedullary tumors.

Cell of origin

Pluripotent stem cell can give rise to eosinophils, neutrophils, monocytes, mast cells, T cells or B cells (16). This was demonstrated by performing nested reverse transcription polymerase chain reaction (RT-PCR), quantitative RT-PCR and FISH studies on purified cell populations from patients presenting with these neoplasms and the fusion gene was detected in eosinophils, neutrophils, mast cells, T cells, B cells and monocytes, suggesting that the mutation arises in a pluripotential hematopoietic progenitor cell capable of giving rise to multiple lineages. The basis for the preferential expansion of eosinophils and mast cells remains unclear.

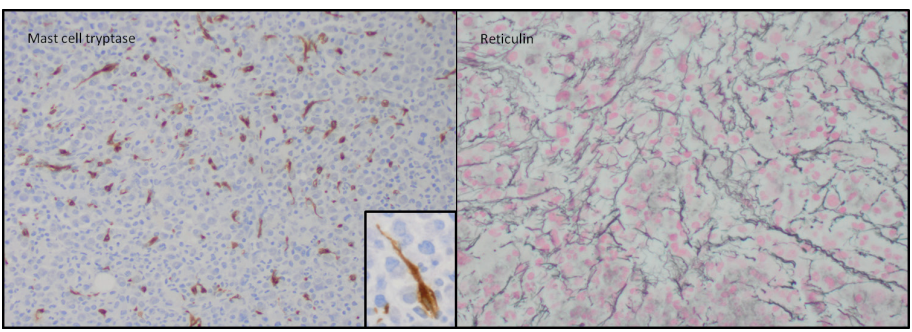

Figure 2. Mast cell. Immunostain highlights increased singly distributed abnormal spindle shaped mast cells. Reticulin stain highlight increased reticulin fiber deposition.

Also, the fusion gene maybe detected in a lineage separate from the presenting neoplasm. For example, lymphocytosis may not be seen even in cases presenting with B or T cell lineage neoplasms (16).

Genetics

The most common genetic variant in the group of M/LN-Eo and *PDGFRA* rearrangement family is the *FIP1L1-PDGFRA* fusion, resulting from a submicroscopic 800-kb interstitial deletion on chromosome 4; del(4)(q12q12). This fusion creates a tyrosine kinase leading to a gain of function event and is responsive to imatinib (4). This fusion is cryptic by karyotype analysis but can be detected by FISH (Figures 3, 4). The FISH test for *FIP1L1-PDGFRA* can be performed by using a three-color probe strategy (*SCFD2*, *LNX*, *PDGFRA*) wherein a deletion of *LNX* (*CHIC2*) locus with retention of the flanking *SCFD2* and *PDGFRA* loci is indicative of the *FIP1L1-PDGFRA* fusion (4, 14). Additional fusion partners of *PDGFRA* that have been described, including *BCR*, *ETV6*, *KIF5B*, *CDK5RAP2*, *STRN*, *TNKS2*, and *FOXP1*. Most *PDGFRA* partner genes can be detected by FISH. Other modalities for detection include next generation sequencing (NGS), RNA fusion assays or if an unbalanced rearrangement suspected; single-nucleotide polymorphism chromosomal microarray approach (SNP-CMA) to detect gains or losses (17).

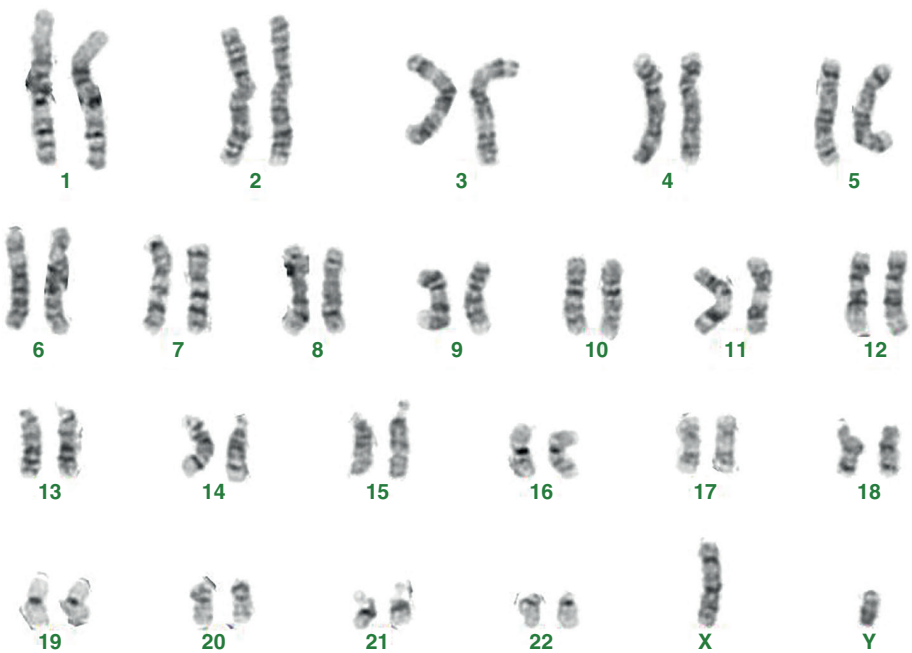

Figure 3. Cytogenetics. The karyotype in M/Ln with Eo and PDGFRA rearrangement is usually normal.

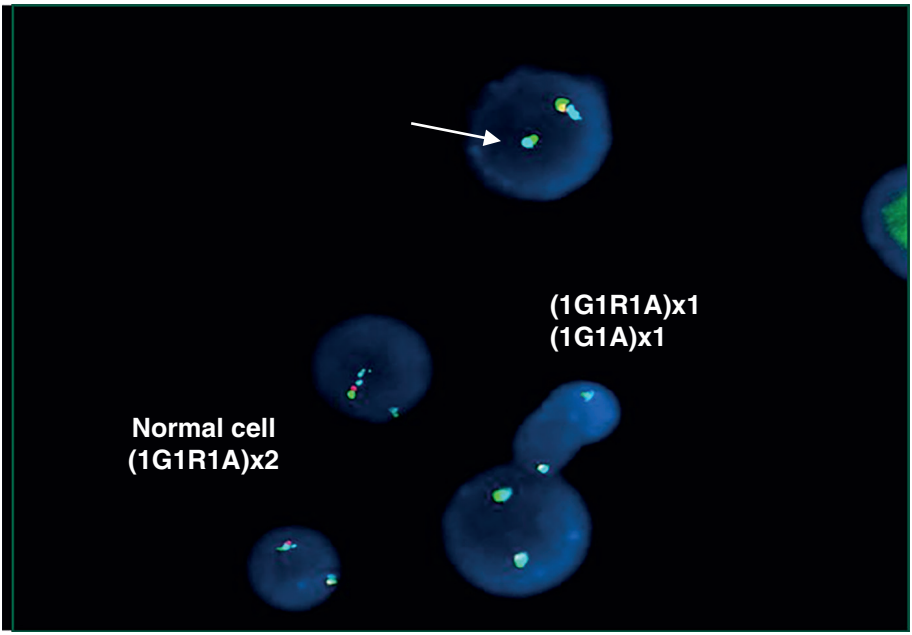

Figure 4. FISH demonstrating a *CHIC2* deletion. FISH performed on fixed nuclei using a tri-color DNA FISH probe strategy (Abbott Molecular) shows a fusion probe signal pattern as a result of a submicroscopic deletion within chromosome 4q12, involving CHIC2. Loss of the spectrum red signal (CHIC2 gene) is noted for one of the two probe signals (arrow). G (green), A (aqua), and R (red) notations refer to the FISH probe spectrum color.

Pathobiology, treatment, and prognosis

M/LN-Eo with abnormalities of *PDGFRA* result from the formation of a fusion gene, or rarely from a mutation resulting in the expression of an aberrant tyrosine kinase. Tyrosine kinase enzymes transfer phosphate from ATP to specific amino acids on substrate proteins (18–23). Phosphorylation of the substrate proteins leads to the activation of signal-transduction pathways that influence cell growth, differentiation, and death. The most studied neoplasm with aberrant tyrosine kinase pathway is chronic myeloid leukemia (CML). This is discussed briefly as its pathobiology is relevant to neoplasms placed in the category of M/LN-Eo with tyrosine kinase fusions, namely *PDGFRA*, *PDGFRB*, *FGFR1*, and *JAK2*, among others defined within this entity.

CML, as we know, is associated with a recurring chromosomal abnormality due to translocation of genetic material with the formation of the Philadelphia chromosome (Ph Chr) (24). The Ph chr is a derivative chromosome 22 resulting from a reciprocal exchange between the long arms of chromosomes 9 and 22 at cytobands 9q34 and 22q11.2. The translocation, t(9;22), results in the juxtaposition of 3' DNA sequences derived from the *ABL* proto-oncogene on chromosome 9 with 5' sequences of the breakpoint cluster region (*BCR*) gene on chromosome 22, forming a fusion well-known as, *BCR-ABL1*. *BCR-ABL1* produces a chimeric

messenger RNA from which a fusion BCR-ABL1 oncoprotein is translated. The length of the BCR-ABL1 chimeric protein varies and is determined by the breakpoint within the *BCR* gene. *ABL1* encodes a tyrosine kinase that is tightly regulated, whereas the activity of BCR-ABL1 fusion protein is autonomous and markedly increased relative to that of normal ABL1 protein. Chronic-phase CML is driven by the constitutively active BCR-ABL1 tyrosine kinase protein, which activates multiple pathways, leading to the malignant expansion of myeloid cells through the stimulation of mitosis, the disruption of cyto-adherence, regulatory control by stromal cells, and the inhibition of apoptosis. Differentiation and maturation of the leukemic clone is relatively intact in chronic-phase CML, however *BCR-ABL1* fusion is also thought to promote genomic instability. This can ultimately lead to secondary mutations and to the blast phase. The BCR-ABL1 oncoprotein activates its substrate by the phosphorylation of one of its tyrosine residues. This subsequently activates other downstream effector molecules. Imatinib mesylate inhibits the tyrosine kinase activity of the BCR-ABL1 oncoprotein, by occupying the ATP binding site whereby the action of BCR-ABL1 is inhibited, preventing phosphorylation of its substrate (18–21, 24, 25).

Given the above historical context of the well-known tyrosine kinase mentioned, the platelet derived growth factor receptor (PDGFR A/B) belongs to a similar family of receptor tyrosine kinase (RTK). PDGFR family of receptors (Figure 5), consist of an extracellular ligand-binding domain, a transmembrane domain, and an intracellular split kinase domain connected by a kinase insert. Ligand binding causes activation, dimerization, and phosphorylation of tyrosine sites. These phosphotyrosines then act as docking sites for Src homology 2 (SH2)

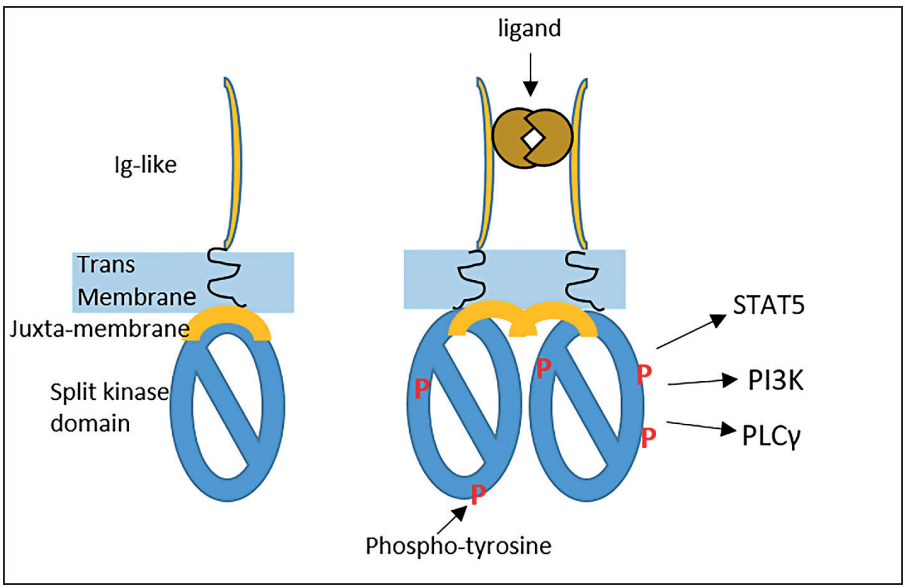

Figure 5. PDGFR A receptor with tyrosine kinase activity. (Adapted from Federica Toffalini, Jean-Baptiste Demoulin, Blood, 2010).

domains of a variety of signal transduction proteins, including phosphatidylinositol 3-kinase (PI3K), phospholipase Cγ (PLCγ), and SRC family kinases, which are shared by type III RTK. A substantial number of adaptor molecules containing SH2 domains, such as Grb2, Grb7, Grb10, Shc, Crk, APS, and Nck provide a diverse set of connections between receptors and signaling pathways, such as mitogen-activated protein. *PDGFR* gene mutations or chimeric proteins resulting from translocations lead to ligand independent constitutive activation of PDGFR. Imatinib mesylate inhibits the tyrosine kinase activity of the mutant PDGFR as well as chimeric PDGFR and other oncoproteins like PDGFRB, cKIT (23, 26–28). In 2003, Cools et al. (4) described an 800kb deletion on chromosome 4q12 which leads to the creation of a *FIP1L1-PDGFRA* fusion gene containing the 5' portion of *FIP1L1* and the 3' portion of *PDGFRA*. This fusion tyrosine kinase receptor is constitutively active and has been shown to induce self-phosphorylation and phosphorylation of the STAT5 pathway (8). The 800kb deletion on chromosome 4q12 display a normal karyotype as mentioned above. However, the *FIP1L1-PDGFRA* fusion may be detected by either RT-PCR or FISH studies (12, 29). As the fusion breakpoints in the *FIP1L1* gene are variable, the size of the product amplified by RT-PCR may vary between patients, and primers must be constructed to account for all known translocation breakpoints. These can be circumvented by the standard quantitative polymerase chain reaction. The screening test is based on detection of overexpression of a 3' region of PDGFRA or a 3' region of PDGFRB which is a possible indicator of an underlying fusion gene. The normal *FIP1L1* and *PDGFRA* genes are closely located on chromosome 4q12 because of which the common "fusion probe" strategy, employed to detect balanced translocations, cannot be used for detection of this abnormality by FISH.

As mentioned earlier, a tri-color FISH strategy is now in use, with one probe located in the 800kb region deleted by the *FIP1L1-PDGFRA* fusion (including the cysteine-rich hydrophobic domain 2 (*CHIC2*) gene and two probes flanking the fusion breakpoints. Deletion of the intervening sequence with retention of the probes telomeric and centromeric to the breakpoint serves as a surrogate marker for the *FIP1L1-PDGFRA* fusion gene. The tri-color FISH method identifies the *FIP1L1/PDGFRA* fusion caused by interstitial deletion of *CHIC2* and other structural rearrangements of *PDGFRA*, albeit the translocation partner may not be readily known, at single cell resolution. Most of these clinical assays are fairly new, especially the PCR assay designed by Erben et al. (30) and well-defined criteria do not exist on the preferred modality for diagnosis and follow-up. The FISH assay is, most times, used for initial diagnosis and RT-PCR assays for follow-up studies or detection of minimal residual disease. There are rare cases where translocations involving the *PDGFRA* gene result in novel chimeric genes (27, 31–34). Other fusion partners of *PDGFRA* include *BCR*, *ETV6*, *KIF5B*, *CDK5RAP2*, *STRN*, *TNKS2*, and *FOXP1*. These translocations can be suggestive by karyotype analysis but require targeted FISH, RT-PCR, or other genomic-scale mapping to identify the partner genes involved. Point mutations in *PDGFRA* have also been identified and are detected by NGS (7, 29, 33, 35). Recognition of this entity is of crucial clinical importance as the *FIP1L1-PDGFRA* fusion protein and the additional translocations involving the *PDGFRA* gene are potently inhibited by imatinib. Low dose (100 mg/day) imatinib therapy in *FIP1L1-PDGFRA* rearrangement positive patients leads to rapid normalization of eosinophil counts, offering the potential to limit the end organ damage (such as endocardial fibrosis) observed in patients

with chronic hypereosinophilia. The neoplasms with *FIP1L1-PDGFRA* are likely responsive also to dasatinib, nilotinib, sorafenib and midostaurin (PKC412) (36). Clinical remission is usually achieved in a month with molecular remission in 3 months. The treatment is not usually discontinued, however there are considerations on potentially limiting or gradually stopping the drug. Of note, resistance to imatinib has also been reported (14, 18, 22, 36, 37).

DIFFERENTIAL DIAGNOSIS OF ENTITIES PRESENTING WITH EOSINOPHILIA

Eosinophils are derived from myeloid progenitors in bone marrow through the action of hematopoietic cytokines such as interleukin (IL)-3, IL-5, and granulocyte-macrophage colony–stimulating factor (GM-CSF). Eosinophils are activated by various stimuli such as tissue injury, viral and bacterial infections, allergens, benign and malignant neoplasms. On activation, eosinophils produce cytotoxic cytostimulatory proteins such as eosinophil peroxidase, major basic protein, eosinophil cationic proteins, cytokines such as Interlukin-2 (IL-2), IL3, IL-4, IL-5, IL-8, Il-10, IL-12, IL-13, and TGF alpha/beta and GM-CSF, chemokines (CCL3/MPI-1alpha, CCL5/RANtes, CCL7/MCP-3, CCL8/MCP-2), lipid mediators (leukotrienes, prostaglandins), and growth factors (heparin-binding epidermal growth factor-like binding protein). These have anti-parasitic and bactericidal activities and modulate immediate allergic reactions and inflammatory responses. However, persistent eosinophilia can result in irreversible organ damage, affecting the heart, lung, skin, gastrointestinal tract, and the central nervous system. Significant cardiovascular complications include endomyocardial fibrosis and intravascular thrombosis (38–40).

Eosinophilia is defined as greater than 0.5 eosinophils × 10^9/L blood. Hypereosinophilia (HE) is defined by >1.5 eosinophils × 10^9/L blood on 2 examinations (interval ≥1 month). Tissue HE is defined by the following: (i) percentage of eosinophils in BM section exceeds 20% of all nucleated cells; and/or (ii) Pathologist is of the opinion that tissue infiltration by eosinophils is extensive; and/or (iii) marked deposition of eosinophil granule proteins (in the absence or presence of eosinophils). Eosinophilia/HE can be seen in reactive conditions such as infections with parasites such as helminth infections, scabies, allergic bronchopulmonary aspergillosis, drug reactions, chronic graft-versus-host disease, chronic inflammatory disorders (e.g., inflammatory bowel disease), autoimmune diseases, pulmonary diseases (e.g., hypersensitivity pneumonitis, Loffler's), and collagen vascular diseases. Secondary HE is usually cytokine driven and is considered a paraneoplastic process due to dysregulated production of IL3, IL5 by the neoplastic cells. It can be seen in Hodgkin's Lymphoma, B- or T-cell lymphoma/leukemia, Langerhans cell histiocytosis or solid tumors/malignancy. Primary or clonal HE is seen in neoplastic hematologic disorders such as CML with eosinophilia, AML with inv(16) and eosinophilia (AML-M4-eo), *JAK2* V617F positive myeloproliferative neoplasm (MPN) with eosinophilia. It is also observed in aggressive systemic mastocytosis, myelodysplastic syndrome or MDS/MPN overlap syndromes with eosinophilia, CEL, hematopoietic neoplasms with eosinophilia and abnormalities in *PDGFRA/B*, *FGFR1* mutations, and lymphocytic variant of

hypereosinophilic syndrome (HES). HES is defined as HE with organ damage such as fibrosis (lung, heart, digestive tract, skin, and others), thrombosis with or without thromboembolism, cutaneous or mucosal erythema, edema/angioedema, ulceration, pruritus, and eczema, as well as peripheral or central neuropathy with chronic or recurrent neurologic deficit. Viewed in terms of the HES, primary HES is analogous to clonal eosinophilia; secondary HES is cytokine driven eosinophilia and idiopathic HES is end-organ damage directly attributable to HE and no discernible underlying cause of the HE (14, 38, 41–43). The algorithm that may be followed for diagnostic evaluation for eosinophilia is shown in Figure 6.

MYELOID/LYMPHOID NEOPLASMS WITH EOSINOPHILIA AND *PDGFRB* REARRANGEMENT

This is a distinct type of myeloid neoplasm that is seen in association with rearrangement of *PDGFRB* at cytoband 5q32, the most common being t(5;12)(q32;p13.2) with formation of the *ETV-PDGFRB* fusion gene. Clinically, it is seen more in males (male-to-female ratio is 2:1) with a wide age range (8–72 years)

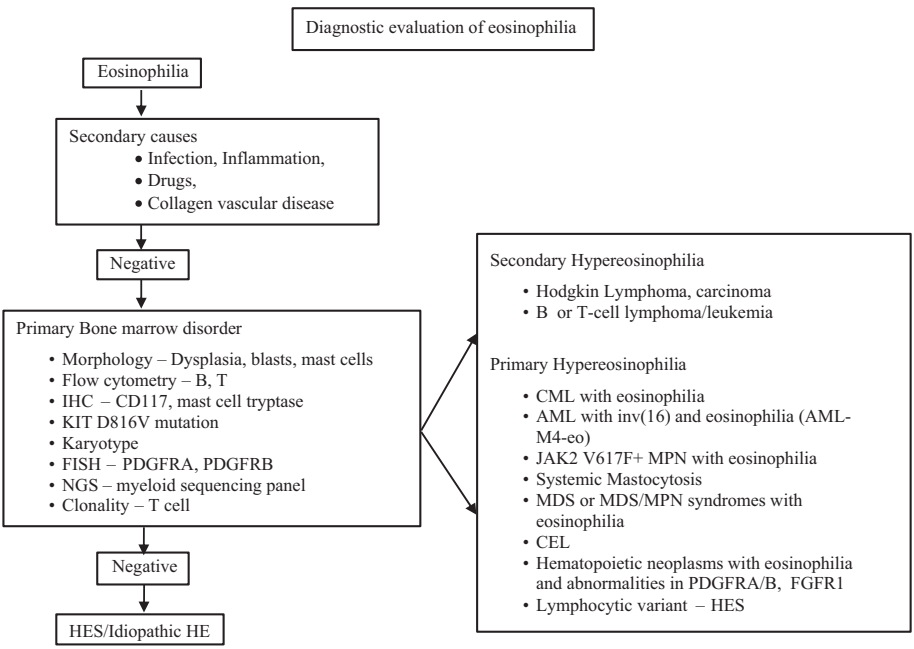

Figure 6. Diagnostic evaluation of eosinophilia. AEC, absolute eosinophil count; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; FISH, fluorescence in situ hybridization; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm; NGS, next-generation sequencing; RT-PCR, reverse transcription polymerase chain reaction. Adapted from Pozdnyakova O, Orazi A, Kelemen K,et al. AmJ Clin Pathol. 2021;155(2):160–78.

and median age of onset in the late 40s. Most present with hepatosplenomegaly, skin infiltration or cardiac disease that may lead to cardiac failure. Serum tryptase is moderately elevated. The hematologic features are most often of CEL or CMML with eosinophilia. Other presentations include aCML with eosinophilia, MPNs with eosinophilia and rarely as AML or juvenile myelomonocytic leukemia (JMML). This entity usually presents with leukocytosis with increased neutrophils, eosinophils, monocytes, and precursors with a median white blood count of 34.4×10^9/L ($6.8–116 \times 10^9$/L) and a median absolute eosinophil count (AEC) of 4.44×10^9/L ($0.07–73.5 \times 10^9$/L). Rarely basophils can be increased. The bone marrow is hypercellular with granulocytic proliferation and eosinophilia. MDS-like megakaryocytes (small hypolobated and forms with abnormal nuclear lobation) are seen whereas MPN-like megakaryocytes are not seen. There can be myelofibrosis and mast cells with spindle-shaped morphology can be seen. These cells can be seen scattered or in loose aggregates, with aberrant CD25 co-expression. Blast are <20% in the peripheral blood or BM. Besides the *ETV6-PDGFRB* gene fusion, at-least 30 additional partner genes have been described with *PDGFRB*, many of which are also imatinib-responsive (7, 14, 28, 44). Cryptic rearrangements are described, in which case FISH/RT-PCR/RNA sequencing can be recommended. Of note, *PDGFRB* fusion genes associated with Ph-like B-ALL are excluded. These Ph-like B-ALL present with *IKZF1* deletion, 7p-, IKZF1/CEP7, rearrangements in *ABL1*, *ABL2, PDGFRB*, JAK2, CRLF2, and *P2RY8*. The screening technique used by Erben et al. (30), is also useful in the detection of these rearrangements (7, 14)). It is important to distinguish Ph-like B-lymphoblastic leukemia/lymphoma from myeloid/lymphoid neoplasms with *PDGFRA*, *PDGFRB* neoplasm. Myeloid/lymphoid neoplasms with Eos cases that present with B-ALL differ from Philadelphia-like B-ALL by the presence of an underlying MPN (7, 14).

MYELOID/LYMPHOID NEOPLASMS WITH EOSINOPHILIA ASSOCIATED WITH *FGFR1* REARRANGEMENT

The aforementioned category has traditionally been considered as stem cell leukemia/lymphoma with rearrangements involving chromosome 8p11 (FGFR1). These are aggressive, rare, pluripotent stem cell disorder with poor prognosis. The WHO 2016 monogram defines these entities as MPN or MDS/MPN with prominent eosinophilia. In some cases, these present with neutrophilia or monocytosis, AML, T- or B-ALL, and/or mixed-phenotype acute leukemia with eosinophilia. The *FGFR1* disease entities can also show the presence of t(8;13)(p11.2;q12) or a variant translocation leading to *FGFR1* rearrangement. These genetic aberrancies can be demonstrated in myeloid cells, lymphoblasts, or both. They usually have multiple partner genes –most often Zn finger gene on chromosome 13. The PB and BM show features of CML, CEL, MPN-unclassifiable, aCML, or MDS/MPN. Somatic mutations are common in *FGFR1*-rearranged cases with *RUNX1* mutations. These do not respond to TKI (imatinib) therapy. Aggressive chemotherapy with stem cell transplant is the best curative option. Newer modalities include Pemigatinib, an FGFR inhibitor are being explored (45, 46).

MYELOID/LYMPHOID NEOPLASMS WITH EOSINOPHILIA AND JAK2 REARRANGEMENTS

These are rare with no more than 30 cases described. These usually present in males with median age of 47 years (1). The most often cited example is t(8;9)(p22;p24.1)/*PCM1-JAK2* that fuses the Janus activated kinase 2 gene (*JAK2*) with the human autoantigen pericentriolar material gene 1 (*PCM1*), resulting in a constitutively activated tyrosine kinase. Structural variants involve *ETV6-JAK2* and *BCR-JAK2* (47). Clinical features are variable with presentation as chronic myeloid neoplasm (MPN/MDS) or acute leukemia (AML, ALL). The morphology shows a triad of features that include hypercellular with eosinophils, aggregates of erythroblasts, and marrow fibrosis. As both myeloid and lymphoid presentation is seen, it is consistent with the origin from pluripotent hematopoietic cells. They can be given targeted therapy with the *JAK2* inhibitor ruxolitinib or stem cell transplant. The *PCM1-JAK2* fusions do not respond to imatinib (45, 46, 48, 49). Nilotinib or dasatinib may be more effective than imatinib to induce durable complete remissions in ETV6-ABL1 positive patients.

The salient features of myeloid/lymphoid neoplasms associated with eosinophilia and tyrosine kinase gene fusions are:

- These arise from pluripotent stem cells as both myeloid & lymphoid proliferations.
- They usually present with eosinophilia.
- These are aberrant tyrosine kinase driven neoplasms and can be treated with tyrosine kinase inhibitors.
- The disease presentations include: MPNs, MDSs, MDS/MPN, AML, B/T-LBL/ALL, or mixed-lineage neoplasms.
- Cryptic rearrangements are recognized in both genes; *PDGFRA, PDGFRB.*
- Cases in these categories of neoplasm that present as B-lymphoblastic lymphoma/leukemia differ from de novo Philadelphia-like B-ALL by the presence of an underlying MPN.

CHRONIC EOSINOPHILIC LEUKEMIA (CEL)

This entity is considered under myeloproliferative neoplasms and not under the umbrella of myeloid/lymphoid neoplasms associated with eosinophilia and rearrangements of *PDGFRA*, *PDGFRB*, *FGFR1,* or *PCM1-JAK2* fusion. CEL, a disease of elderly males, who may present asymptomatic or with constitutional symptoms such as weight loss, night sweats, fever, angio-edema, and other features seen in patients with eosinophilia. As defined by the WHO 2016, the diagnostic criteria include:

(i) Eosinophilia ($>1.5 \times 10^3/\mu L$) for at least 4 weeks
(ii) Exclude BCR-ABL1+ CML, PV, ET, PMF, CNL, CMML, aCML,
(iii) Exclude PDGFRA, PDGFRB, FGFR1, PCM-JAK2, ETV-JAK2, BCR-JAK2 fusion.

(iv) Blasts are <20% of all cells (No diagnostic features of AML with inv(16) (p13.1q22), t(16;16) (p13.1q22), t(8;21)(q22;q22.1), and other diagnostic features of AML are present)
(v) Demonstrate morphology and cytogenetic and/or molecular genetic abnormality or blasts >2% in PB, or >5% and <19% in BM. As per the latest WHO 5th edition the criteria of increased blasts (≥2% in peripheral blood or 5–19% in bone marrow) as an alternative to clonality is eliminated (1).

The most striking feature is peripheral blood eosinophilia on microscopy are mostly mature forms and rarely immature forms of eosinophilic myelocytes and promyelocytes. Eosinophils may show sparse granulation, cytoplasmic vacuolation, hyper or hypo segmentation, but are not specific to the disease and can be seen in reactive conditions as well. The bone marrow is hypercellular with dysplasia that can be seen in megakaryocytes, erythroid precursors, or granulocytes. A recent paper by Wang et al. provide more specific criteria that can help in separating this entity from reactive etiologies, such as dysplasia in megakaryocytes, and erythroids and granulocyte in greater than 20% of the cells (15). In addition, any of the following two features can help in separating the entities: hypercellularity (>20–30% age appropriate), abnormal eosinophils, myelofibrosis, or G: E ratio>10 (15). Evidence of cytogenetic, FISH, and molecular clonality may include trisomy 8 or isochromosome 17 [i(17q)], loss of chromosome 7. Somatic mutation in *ASXL1*, *TET2*, *E2Z2*, *KIT*, *M541L*, X-linked polymorphism of HUMARA and *PGK* genes or variants that have been seen in other myeloid neoplasms such as *TP53*, *EZH2*, *SETBP1*, *NRAS*, *CSF3R*, *JAK2* are also observed (50). CEL is diagnosed when all reactive etiology for eosinophilia has been excluded and there is no evidence of a lymphoproliferative or myeloproliferative disorder. The positive criteria for diagnosis of CEL is demonstration of morphologic abnormality and a clonal chromosomal abnormality. Given that the identification of a *FIP1L1-PDGFRA* fusion gene provides evidence for a clonal population of eosinophils, neoplasms with *PDGFRA-FIP1L1* fusions were initially also classified as CEL, before the separate categorization for MLN TK was introduced in WHO 2008. It is worth noting that a subset of patients with HES/CEL, without well-defined genetic abnormality, also respond to imatinib therapy. They presumably possess other, not-yet characterized, tyrosine kinase abnormalities that drive the HE (4, 29, 51, 52). Patients with CEL are usually treated with hydroxyurea, interferon-α or allo hematopoietic stem cell transplant (HSCT) (6, 15).

LYMPHOCYTIC VARIANT OF HES

Persistent HE has been seen in a subset of patients that show abnormal T-lymphocytes identified either phenotypically by flow cytometry or clonal T-cell populations as delineated by PCR and considered as a 'lymphoproliferative variant' of HE. Briefly, the normal CD4+ T helper cells are divided into Th1, Th2 cells. Th1 secrete interleukin-2 (IL2), interferon gamma, and tumor necrosis factor and are involved in cell-mediated immunity. Th2 secrete IL4 (i.e., it stimulates the production of IgE antibodies) and IL5 (i.e., promotes the differentiation and activation of eosinophils). In some patients, there is expansion of an abnormal proliferation of Th2 type cells,

through production of IL-5 and other cytokines is thought to contribute to persistent eosinophilia. The T cells are phenotypically abnormal and reported aberrancies are (CD2+/3+/4+/5+/7↓↓); (CD2+/3+/7+/8+/5↓↓), (CD2+/4+/3–/7–), $CD3^{+}4^{-}8^{-}\alpha\beta^{+}$). They are clonal as demonstrated by karyotype analysis and instability of 6q, partial 6q or 10p deletions have been reported. T cell receptor gene rearrangements are also seen. It is currently unclear whether these T cell proliferations represent unusual reactive processes or are possibly early peripheral blood involvement by a subtle T-cell lymphoma or leukemia. Clinically these patients present with cutaneous lesions, pruritus, erythroderma, urticarial, angioedema, serum hyper IgE, and polyclonal hypergammaglobulinemia. There is no standard therapy for lymphoproliferative variant of eosinophilia. However, use of corticosteroid therapy along with low-dose oral cyclophosphamide or methotrexate as steroid-sparing agents has been reported (52–54).

SYSTEMIC MASTOCYTOSIS WITH EOSINOPHILIA

Mastocytosis is a rare neoplasm and includes three disease types: systemic mastocytosis (SM), cutaneous mastocytosis and mast cell sarcoma. SM is a clonal disorder of mast cells characterized by involvement of at least one extracutaneous organ, with or without evidence of skin lesions. The constellation of clinical features includes gastrointestinal symptoms, cutaneous symptoms, splenomegaly, anemia, and a subset of cases of SM may present with eosinophilia. The diagnosis of SM is based on the presence of one major and one minor, or 3 minor criteria. The major criterion is defined by the presence of two or more dense mast cell aggregates (>15 mast cells/aggregate) in bone marrow or extracutaneous organ. Minor criteria include the presence of >25% spindled, immature or atypical mast cells; *KIT* point mutation at codon 816; or aberrant expression of CD2, +/- CD25, +/-CD30 on mast cells or serum tryptase greater than >20 ng/mL.

Some of the P*DGFRA/FIP1L1* positive MPNs present with spindled, CD25+ mast cells and elevated tryptase levels, and therefore may meet the three minor criteria used for the diagnosis of systemic mastocytosis. These have, in the past been delineated as systemic mastocytosis with *FIP1L1-PDGFRA* fusion (9, 13). One large study, however, highlighted distinct clinical and biological differences between neoplasms with *FIP1L1-PDGFRA* rearrangements and cases diagnostic for systemic mastocytosis (11, 13). In particular, *FIP1L1-PDGFRA*+ cases display a marked male predominance, with cardiac and pulmonary symptoms being more common and gastrointestinal symptoms being less common than in systemic mastocytosis, irrespective of eosinophilia. While tryptase levels are often elevated in *FIP1L1-PDGFRA*+ patients, the elevation is moderate (usually <50 ng/mL) in contrast to systemic mastocytosis which frequently displays tryptase levels >100 ng/mL. Finally, the *KIT* codon 816 mutations typical of systemic mastocytosis are not identified in *FIP1L1-PDGFRA* positive cases. The demonstration of distinct clinical, morphologic, and genetic features in *FIP1L1-PDGFRA*+ cases warrant their distinction from systemic mastocytosis. The current WHO classification has therefore recognized *FIP1L1-PDGFRA*+ myeloproliferative neoplasm as a distinct clinicopathologic entity based on molecular pathogenesis and molecularly targeted therapy (1).

CONCLUSION

This chapter defines criteria for *PDGFRA*-associated myeloid/lymphoid neoplasms. Entities included within Myeloid/Lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions are discussed with reference to the latest edition of WHO classification of tumors of hematopoietic and lymphoid tissues (5th edition 2022). The current technologies including FISH use for the diagnosis are discussed. Finally, the differential diagnosis of entities that present with eosinophilia are discussed.

Conflict of Interest: The authors declare no potential conflict of interest with respect to research, authorship and/or publication of this chapter.

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