OVERVIEW\textsuperscript{1,2,3,4,5}

Clonal eosinophilia associated with tyrosine kinase (TK) fusion gene rearrangements (PDGFR\textalpha, PDGFR\beta, FGFR1, JAK2, ABL1, or FLT3) can have diverse clinical presentations including Ph-negative myeloproliferative neoplasms (MPN) with eosinophilia, myelodysplastic syndromes (MDS)/MPN with eosinophilia, acute myeloid leukemia (AML), B-cell or T-cell lymphomas, acute lymphoblastic leukemia (ALL), or mixed lineage leukemias/lymphomas.

A diagnosis of myeloid/lymphoid neoplasms with eosinophilia should be suspected in the following clinical situations (See MLNE-1):
• Sustained eosinophilia (≥1.5 x 10\textsuperscript{15/L}) or tissue eosinophilia (any eosinophil count) in a target organ, with the occurrence of characteristic genetic breakpoints, with some not always visible by standard cytogenetics (eg, FIP1L1-PDGFR\textalpha, ETV6-ABL1);
• Clinical features such as splenomegaly, anemia, thrombocytopenia, leukoerythroblastosis, circulating dysplastic cells, elevated serum vitamin B12 and/or tryptase levels, and abnormal mast cell proliferation in the bone marrow (BM);
• Features of systemic mastocytosis (SM) with eosinophilia but with interstitial, not dense aggregates of atypical mast cells (FIP1L1-PDGFR\textalpha rearrangement);
• Features of chronic myelomonocytic leukemia (CMML) with eosinophilia (PDGFR\beta rearrangement);
• Persistent eosinophilia after intensive treatment of AML, ALL, B-cell lymphoma, or T-cell lymphoma.

Myeloid/Lymphoid Neoplasms with Eosinophilia and FIP1L1-PDGFR\textalpha Rearrangement:

Chronic eosinophilic leukemia (CEL) is the most common clinical presentation. Variant presentations include blast phase MPN, AML with eosinophilia, or rarely T-cell ALL (T-ALL) with FIP1L1-PDGFR\alpha or myeloid sarcoma. This entity has a strong male predominance and is commonly associated with marked elevation of serum vitamin B12, elevated serum tryptase, and splenomegaly. Peripheral eosinophilia is usually, but not always, observed. BM is hypercellular with increased eosinophil precursors (generally without dysplasia) and proliferation of loosely distributed CD25+ spindle-shaped mast cells. Dense clusters of mast cells typically seen in SM with the KIT D816V mutation are usually absent.

Myeloid/Lymphoid Neoplasms with Eosinophilia and PDGFR\beta Rearrangement:

CMML, atypical CML, MDS/MPN, MPN, juvenile myelomonocytic leukemia (JMML), and blast phase disease involving the BM and/or extramedullary disease (EMD) involving myeloid, lymphoid, or mixed lineages. This entity also has a strong male predominance. Eosinophilia is not invariably present.

Myeloid/Lymphoid Neoplasms with Eosinophilia and FGFR1 Rearrangement:

MPN with eosinophilia, AML, B-cell or T-cell lymphoma/ALL mixed phenotype acute leukemia, and/or EMD of myeloid, lymphoid, or mixed lineage. This entity has a moderate male predominance and is generally associated with an aggressive clinical course with rapid progression of chronic phase disease to blast phase/secondary acute leukemia. Eosinophilia is not invariably present.
**OVERVIEW**\(^1,3,4,5\)

**Myeloid/Lymphoid Neoplasms with Eosinophilia and JAK2 Rearrangement:**

Chronic myeloid neoplasm with eosinophilia (MPN with eosinophilia or MDS/MPN with eosinophilia) is the characteristic clinical presentation. ALL or de novo AML have also been observed. This entity has a strong male predominance and is generally associated with an aggressive clinical course with rapid progression of chronic phase disease to blast phase/secondary acute leukemia. The presence of eosinophilia is more variable for BCR-JAK2 and ETFV6-JAK2 variants.

**Myeloid/Lymphoid Neoplasms with Eosinophilia and FLT3 or ABL1 Rearrangement:**

Myeloid and/or lymphoid neoplasm with eosinophilia, consistent with the WHO category of CEL not otherwise specified (CEL-NOS) is the characteristic clinical presentation associated with FLT3 rearrangement. Peripheral T-cell lymphoma or T-cell lymphoblastic lymphoma (T-LBL) have also been described. De novo ALL is the most common clinical presentation associated with ABL1 rearrangement; however, various acute leukemia and chronic myeloid/lymphoid phenotypes have also been described. It is generally associated with an aggressive clinical course, disease progression, or relapse. Eosinophilia is not invariably present.

**References**

2017 WHO DIAGNOSTIC CRITERIA FOR MYELOID/LYMPHOID NEOPLASMS WITH EOSINOPHILIA AND REARRANGEMENT OF PDGFRα, PDGFRβ, OR FGFR1, OR WITH PCM1-JAK2

Myeloid/Lymphoid Neoplasms with Eosinophilia Associated with FIP1L1-PDGFRα or a Variant Fusion Gene*  
A myeloid or lymphoid neoplasm, usually with prominent eosinophilia and:
Presence of a FIP1L1-PDGFRα fusion gene or a variant fusion gene with rearrangement of PDGFRα or an activating mutation of PDGFRα†

Myeloid/Lymphoid Neoplasms with Eosinophilia Associated with ETV6-PDGFRB or Other Rearrangement of PDGFRB†  
A myeloid or lymphoid neoplasm, often with prominent eosinophilia and sometimes with neutrophilia or monocytosis and:
Presence of t(5;12)(q31;q33)p13) or a variant translocation† or demonstration of an ETV6-PDGFRB fusion gene or other rearrangement of PDGFRB

Myeloid/Lymphoid Neoplasms with Eosinophilia Associated with FGFR1 Rearrangement  
A myelodysplastic/myeloproliferative neoplasm with prominent eosinophilia, and sometimes with neutrophilia or monocytosis or Acute myeloid leukemia or T-cell or B-cell lymphoblastic leukemia/lymphoma or mixed phenotype acute leukemia (usually associated with peripheral blood or bone marrow eosinophilia) and:
Presence of t(8;13)(p11;q12) or a variant translocation leading to FGFR1 rearrangement demonstrated in myeloid cells, lymphoblasts, or both

Myeloid/Lymphoid Neoplasms with Eosinophilia Associated with PCM1-JAK2 Rearrangement  
A myeloid or lymphoid neoplasm, often with prominent eosinophilia and:
Presence of t(8;9)(p22.1;p24.1) or a variant translocation leading to JAK2 rearrangement§

*Patients presenting with myeloproliferative neoplasm, acute myeloid leukemia, or lymphoblastic leukemia/lymphoma with eosinophilia and a FIP1L1-PDGFRα fusion gene are also assigned to this category.
†If appropriate molecular analysis is not possible, this diagnosis should be suspected if there is a Ph-chromosome–negative myeloproliferative neoplasm with the hematologic features of chronic eosinophilic leukemia associated with splenomegaly, a marked elevation of serum vitamin B12, elevation of serum tryptase, and an increased number of bone marrow mast cells.
§Cases with fusion genes typically associated only with BCR-ABL1-like B-lymphoblastic leukemia are specifically excluded.

†Because t(5;12)(q31;q33)p13) does not always lead to an ETV6-PDGFRB fusion gene, molecular confirmation is highly desirable. If molecular analysis is not possible, this diagnosis should be suspected if there is a Ph chromosome–negative myeloproliferative neoplasm associated with eosinophilia and with a translocation with a 5q31;33 breakpoint.
§Other variants giving rise to a fusion gene between JAK2 and an alternative partner include ETV6-JAK2 [t(9;12)(p24.1;p13.2)] or BCR-JAK2 [t(9;22)(p24.1;q11.2)].

PRINCIPLES OF CYTOGENETIC AND MOLECULAR TESTING IN MYELOID/LYMPHOID NEOPLASMS WITH EOSINOPHILIA
AND TYROSINE KINASE FUSION GENES

REFERENCES

2. Golib J, Cools J. Five years since the discovery of FIP1L1-PDGFR: what we have learned about the fusion and other molecularly defined eosinophilias Leukemia 2008;22:1999-2010.