TABLE 135e-6 DIAGNOSIS OF CHRONIC EOSINOPHILIC LEUKEMIA AND HYPEREOSINOPHILIC SYNDROME

Required: Persistent eosinophilia ≥1500/μL in blood, increased marrow eosinophils, and myeloblasts <20% in blood or marrow.

1. Exclude all causes of reactive eosinophilia: allergy, parasites, infection, pulmonary disease (e.g., hypersensitivity pneumonitis, Loeffler's), and collagen vascular diseases
2. Exclude primary neoplasms associated with secondary eosinophilia: T-cell lymphomas, Hodgkin's disease, acute lymphoid leukemia, mastocytosis
3. Exclude other primary myeloid neoplasms that may involve eosinophils: chronic myeloid leukemia, acute myeloid leukemia with inv(16) or t(16;16)(p13;q22), other myeloproliferative syndromes, and myelodysplasia
4. Exclude T-cell reaction with increased interleukin 5 or other cytokine production

If these entities have been excluded and no evidence documents a clonal myeloid disorder, the diagnosis is hypereosinophilic syndrome.

If these entities have been excluded and the myeloid cells show a clonal chromosome abnormality or some other evidence of clonality and blast cells are present in the peripheral blood (>2%) or are increased in the marrow (but <20%), the diagnosis is chronic eosinophilic leukemia.

with MPN-U, whereas patients with arterial thrombotic complications might require cytoreductive and aspirin therapy and those with venous thrombosis might require systemic anticoagulation.

TRANSIENT MYELOPROLIFERATIVE DISORDER (TMD)

TMD constitutes an often but not always transient phenomenon of abnormal megakaryoblast proliferation, which occurs in approximately 10% of infants with Down's syndrome. TMD is usually recognized at birth and either undergoes spontaneous regression (75% of cases) or progresses into acute megakaryoblastic leukemia (AMKL) (25% of cases). Almost all patients with TMD and TMD-derived AMKL display somatic *GATA1* mutations. TMD-associated *GATA1* mutations constitute exon 2 insertions, deletions, or missense mutations, affecting the N-terminal transactivation domain of GATA-1, and result in loss of full-length (50-kDa) GATA-1 and its replacement with a shorter isoform (40-kDa) that retains friend of GATA-1 (FOG-1) binding. In contrast, inherited forms of exon 2 *GATA1* mutations produce a phenotype with anemia, whereas exon 4 mutations that affect the N-terminal, FOG-1-interactive domain produce familial dyserythropoietic anemia with thrombocytopenia or X-linked macrothrombocytopenia.

EOSINOPHILIC DISORDERS

Eosinophilia refers to a peripheral blood absolute eosinophil count (AEC) that is above the upper normal limit of the reference range. The term *hypereosinophilia* is used when the AEC is >1500 × 10^9/L. Eosinophilia is operationally classified as secondary (nonneoplastic proliferation of eosinophils) and primary (proliferation of eosinophils that is either neoplastic or otherwise unexplained) (Table 135e-6). Secondary eosinophilia is by far the most frequent cause of eosinophilia and is often associated with infections, especially those related to tissue-invasive helminths; allergic/vasculitic diseases; drugs; and metastatic cancer. Primary eosinophilia is the focus of this chapter and is considered when a cause for secondary eosinophilia is not readily apparent.

Primary Eosinophilia Primary eosinophilia is classified as clonal or idiopathic. Diagnosis of clonal eosinophilia requires morphologic, cytogenetic, or molecular evidence of a myeloid neoplasm. Idiopathic eosinophilia is considered when both secondary and clonal eosinophilias have been ruled out as a possibility. HES is a subcategory of idiopathic eosinophilia with persistent AEC of ≥1.5 × 10^9/L and associated with eosinophil-mediated organ damage (Table 135e-7). An HES-like disorder that is associated with clonal or phenotypically abnormal T cells is referred to as *lymphocytic variant hypereosinophilia* (Table 135e-7).

Clonal Eosinophilia Examples of clonal eosinophilia include eosinophilia associated with acute myeloid leukemia (AML), MDS, CML, mastocytosis, and MDS/MPN overlap. Myeloid neoplasm-associated eosinophilia also includes the WHO MPN subcategory of chronic eosinophilic leukemia, not otherwise specified (CEL-NOS) and the WHO myeloid malignancy subcategory referred to as myeloid/lymphoid neoplasms with eosinophilia and mutations involving platelet-derived growth factor receptor (*PDGFR*) α/β or fibroblast growth factor receptor 1 (*FGFR1*).

The diagnostic workup for clonal eosinophilia that is not associated with morphologically overt myeloid malignancy should start with peripheral blood mutation screening for *FIP1L1-PDGFRA* and *PDGFRB* mutations using fluorescence in situ hybridization (FISH) or reverse transcription polymerase chain reaction. This is crucial because such eosinophilia is easily treated with imatinib. If mutation screening is negative, a bone marrow examination with cytogenetic studies is indicated. In this regard, one must first pay attention to the presence or absence of 5q33, 4q12, or 8p11.2 translocations, which, if present, would suggest *PDGFRB*-, *PDGFRA*-, or *FGFR1*-rearranged clonal eosinophilia, respectively. The presence of 5q33 or 4q12 translocations predicts favorable response to treatment with imatinib mesylate, whereas 8p11.2 translocations are associated with aggressive myeloid malignancies that are refractory to current drug therapy.

CEL-NOS is considered in the presence of cytogenetic/morphologic evidence of a myeloid malignancy that is otherwise not classifiable. Specifically, CEL-NOS is distinguished from HES by the presence of either a cytogenetic abnormality or greater than 2% peripheral blood blasts or greater than 5% bone marrow blasts (Table 135e-7). HES or idiopathic eosinophilia is considered in the absence of both morphologic and molecular evidence of clonal eosinophilia. However, before making a working diagnosis of HES, one has to exclude lymphocytic variant hypereosinophilia by excluding the presence of phenotypically abnormal T lymphocytes (by flow cytometry) and clonal T-cell gene rearrangements.

Chronic Eosinophilic Leukemia, Not Otherwise Specified (CEL-NOS) CEL-NOS is a subset of clonal eosinophilia that is neither molecularly defined nor classified as an alternative clinicopathologically assigned myeloid malignancy. We prefer to use the term strictly in patients with an HES phenotype who also display either a clonal cytogenetic/molecular abnormality or excess blasts in the bone marrow or peripheral blood. The WHO defines CEL-NOS in the presence of an AEC ≥1.5 × 10^9/L

TABLE 135e-7 PRIMARY EOSINOPHILIA CLASSIFICATION

Variables	*PDGFRA*-, *PDGFRB*-, or *FGFR1*-Mutated Eosinophilia	Chronic Eosinophilia, Not Otherwise Specified	Lymphocytic Variant Hypereosinophilia	Hypereosinophilic Syndrome
Absolute eosinophil count	>600 ×10^9/L	>1500 × 10^9/L	>1500 × 10^9/L	>1500 × 10^9/L
Peripheral blood blast >2%	Yes or no	Yes or no	No	No
Bone marrow blast >5%	Yes or no	Yes or No	No	No
Abnormal karyotype	Yes or no	Yes or no	No	No
PDGFRA, *PDGFRB*, or *FGFR1* mutation	Yes	No	No	No
BCR-ABL1	No	No	No	No
Abnormal T lymphocyte phenotype or clonal T-cell clones	No	No	Yes	No
Eosinophil-mediated tissue damage	Yes or no	Yes or no	Yes or no	Yes