Atlas of Genetics and Cytogenetics
in Oncology and Haematology

OPEN ACCESS JOURNAL

INIST-CNRS

Leukemia Section
Review

Chronic Eosinophilic Leukemia-Not Otherwise Specified (CEL-NOS)

Idiopathic Hypereosinophilic Syndrome (IHES)

Anwar N. Mohamed

Cytogenetics Laboratory, Pathology Department, Detroit Medical Center, Wayne State University School of Medicine, Detroit, MI USA. amohamed@dmc.org

Published in Atlas Database: June 2018
Online updated version : http://AtlasGeneticsOncology.org/Anomalies/ChrEosinoLeukID1340.html
Printable original version : http://documents.irevues.inist.fr/bitstream/handle/2042/70027/06-2018-ChrEosinoLeukID1340.pdf
DOI: 10.4267/2042/70027

This work is licensed under a Creative Commons Attribution-Noncommercial-No Derivative Works 2.0 France Licence.
© 2019 Atlas of Genetics and Cytogenetics in Oncology and Haematology

Abstract

Chronic eosinophilic leukemia (CEL) not otherwise specified (NOS) and idiopathic hypereosinophilic syndrome (HES) are rare hematologic disorders characterized by chronic, unexplained eosinophilia with manifestation of organ involvement related to eosinophil infiltration, in the absence of evidence of secondary causes such as parasitic infestation, allergy, or neoplasm. Neither CEL-NOS nor idiopathic HES show Ph chromosome/ BCR-ABL fusion gene or other genetically defined entities such as PDGFRA, PDGFRB, or FGFR1 abnormalities.

Keywords
Chronic eosinophilic syndrome, hypereosinophilia, CEL-NOS, idiopathic HES

Clinics and pathology

Disease

Chronic Eosinophilic Leukemia not otherwise specified (CEL-NOS)
CEL-NOS is a myeloproliferative neoplasm caused by autonomous clonal proliferation of eosinophilic precursors that result to increased number of eosinophils in peripheral blood, bone marrow and peripheral tissues with eosinophilia being the most striking feature. The key criteria for diagnosis of CEL-NOS are peripheral blood hypereosinophilia (>1.5 -10 ^{9}/L), an increased number of myeloblasts in blood and bone marrow (

The diagnostic criteria of CEL-NOS based on the revised WHO 2016 include:

1 Marked eosinophilia, count of ≥ 1.5x109/L in peripheral blood persisting for more than 6 months

2 An increase of myeloblasts in peripheral blood >2% or bone marrow myeloblasts < 20% of all nucleated cells

3 There is an evidence of clonality of eosinophils verified by detection of clonal cytogenetic or molecular genetic abnormality, or by demonstration of skewed expression of X chromosome genes

4 Does not meet the WHO diagnostic criteria for chronic myeloid leukemia (CML), or other myeloproliferative neoplasms (PV, ET, PMF, systemic mastocytosis) or MDS/MPN (CMML or atypical CML)

5 No t(9;22) BCR / ABL1 fusion; No rearrangement of PDGFRA, PDGFRB, or FGFR1; no PCM1 / JAK2, ETV6 /JAK2, or BCR/JAK2 fusion gene

6 No inv(16) / CBFB rearrangement and other diagnostic features of acute myeloid leukemia (AML).

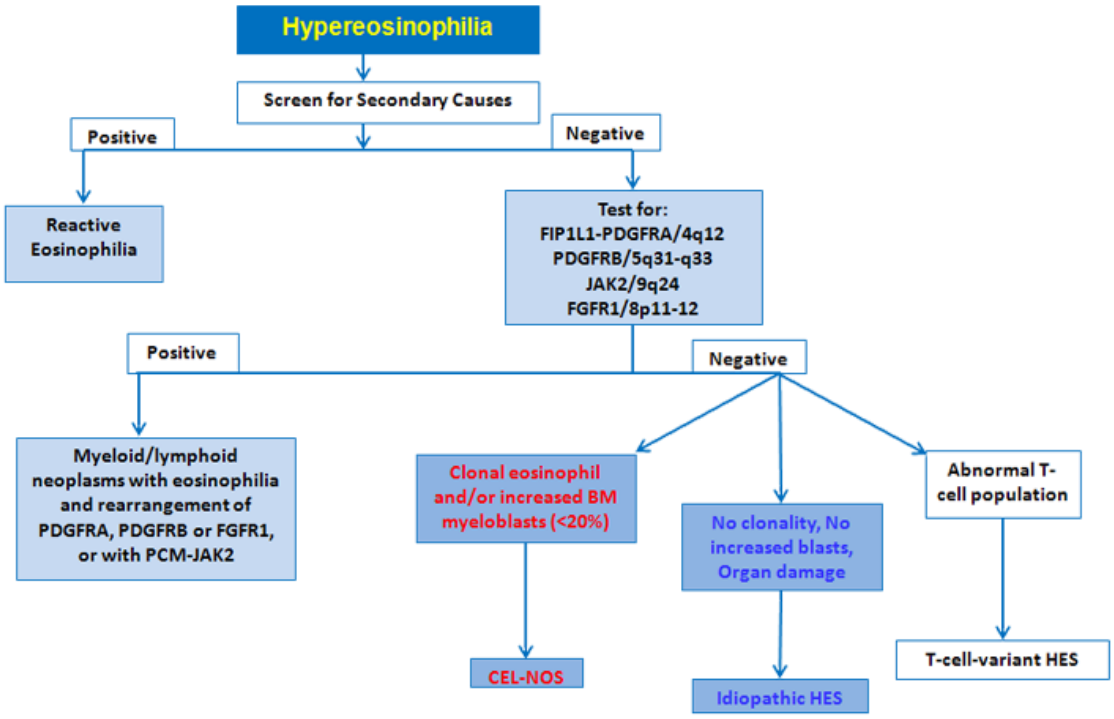

Figure 1; Diagnostic algorithm of CEL-NOS and Idiopathic HES based on WHO 2016 criteria

Idiopathic hypereosinophilic syndrome (IHES)

If clonality of eosinophils cannot be proven and there is no increase in myleoblasts, then the diagnosis is idiopathic HES (Bain et al, 2016). Idiopathic HES is a diagnosis of exclusion when secondary and clonal causes of eosinophilia are ruled out (Bain, 2004 A; Bain, 2004B). It is defined as sustained eosinophilia $\geq 1.5X10^{9}$ in peripheral blood for at least 6 months with signs of organ involvement and dysfunction in which the underlying cause remains unknown (Figure 1). There is no increase in blasts and no evidence of eosinophil clonalilty. Yet, the advances in molecular diagnostic technologies have demonstrated that many patients who had previously been considered as having idiopathic HES can now be found to have an eosinophilic leukemia since clonal molecular genetic abnormality can be demonstrated (Gotlib and Cools 2008). Moreover, transformation to acute myeloid leukemia in some patients with idiopathic HES also provides evidence that the disorder was likely from the start to be a clonal CEL (Wang et al, 2016).

Epidemiology

The incidence of CEL-NOS is not well-defined due to rarity of the disorders and difficulty to distinguish CEL-NOS from idiopathic HES. Recently reported study using the Surveillance, Epidemiology, and End Results shows an incidence of 0.036 per 100,000 person-years, but this calculation included patients with HES and other clonal CEL (Crane et al, 2010). CEL-NOS affect more males than females with a reported median age of diagnosis in the sixty (Bain et al, 2016; Wang et al 2016). The epidemiology features of idiopathic HES remain undefined.

Clinics

Patients may present with various combinations of symptoms and signs of end-organ damage mediated by eosinophils. In many patients, the onset of symptoms is insidious, and eosinophilia is detected incidentally. However in others, the initial manifestations are severe and life-threatening due to the rapid progression of cardiovascular or neurologic complications. The common constitutional symptoms that patients experience are fatigue, cough, dyspnea, myalgia, fever, diarrhea, rash and/or rhinitis. Progressive heart failure is an example of eosinophil-mediated organ injury which is the major cause of morbidity and mortality in these patients. Endocardial damage with resulting platelet thrombus can lead to mural thrombi and increased embolic risk. In the later fibrotic stage, endomyocardial fibrosis can evolve to a restrictive cardiomyopathy, and insufficiency of the mitral and tricuspid valves. Pulmonary disease affects up to 50% of those patients. Pulmonary infiltrates and fibrosis may develop focal or diffuse. Hematologic manifestations are largely nonspecific and may include fatigue, which may be due to the anemia. Thrombotic episodes due to cardiac injury or caused by hypercoagulability occur frequently and often present as neurologic symptoms. CNS dysfunction, peripheral neuropathy, GI disorders and skin lesions are also frequent manifestations (Gotlib 2015, Gotlib 2017).

Cytology

The most remarkable feature in the peripheral blood is hypereosinophilia usually greater than $1.5x10^9$ /L. The leukocyte count is often moderately elevated between 20,000-30,000/μL, and eosinophils in most instances account for 30%-70% of the differential counts. The blood exhibits mature eosinophils with only a small number of eosinophilic myelocytes or promyelocytes. A range of eosinophil abnormalities may be seen such as sparse granulation, cytoplasmic vaculation, small or immature granules, nuclear hypersegmentation or hyposegmentation. Some patients may show monocytosis, mild basophillia or increased blasts. Anemia and thrombocytopenia may be present (Gotlib, 2017).

The bone marrow is usually hypercellular and shows eosinophilic hyperplasia. Eosinophil counts may range from 10% -70% of the bone marrow nucleated cells, with an average of 30%. The maturation of eosinophils and myeloid cells is progressive but often left-shifted with increased blasts (5%-19%). Charcot-Leyden crystals are frequently seen which are colorless crystals formed from the breakdown of eosinophils. Eosinophils may show dysplastic changes such as nuclear hypersegmentation or hyposegmentation, cytoplasmic vacuolization or hypogranularity, and/or abnormal eosinophilic granules. Still, these morphologic changes and Charcot-Leyden crystals are not specific for CEL since may be seen in reactive eosinophilia. Marrow fibrosis is seen in some cases (Bain et al, 2016). Eosinophilic infiltration may also be present in extramedullary tissues, most frequently involving skin, heart, lung, nervous system and gastrointestinal (GI) tract. Organ damage induced by eosinophilic infiltration is due to the release of eosinophil granules which contain toxic cationic proteins, the primary mediators of tissue damage. The site of infiltration usually shows some degree of fibrosis, often with the presence of Charcot-Leyden crystals.

Cytogenetics

Both CEL-NOS and idiopathic HES require the exclusion of the genetically defined eosinophilic neoplasms specifically cases with rearrangements of PDGFRA, PDGFRB, FGFR1, PCM1/JAK2 or variants [Figure 1]. In rare cases, the finding of Ph chromosome/BCR-ABL fusion indicates CML with dominant eosinophilia. No specific cytogenetic abnormality has been identified in CEL-NOS. Nevertheless, chromosomal abnormalities associated myeloid neoplasms such as trisomy chromosome 8, deletion of chromosome 7/7q, isochromosome 17q, and complex karyotype are frequently observed which indicate clonality and support the diagnosis of CEL-NOS. Humara test, X-linked polymorphism, has been used in female patients to demonstrate clonality.

Treatment

Various agents are often used sequentially over the course of disease for treatment of CEL-NOS and idiopathic HES. Corticosteroid is the first-line therapy that induces remission in over 80% of patients. Hydroxyurea, and interferon alpha are also effective but are limited by their toxicity (Ogbogu et al, 2009). Alemtuzumab, an anti-CD52 monoclonal antibody, has been shown to control symptoms as well as eosinophilia in patients with refractory hypereosinophilic syndrome. Response to tyrosine kinase inhibitors, such as Imatinib is uncommon. High dose chemotherapy has been in used in some patients when disease showed progression. For those patients who fail the available pharmacologic therapies, stem cell transplant offers the potential for long-term remission and possible cure. In addition, patients may require interventions for specific cardiac complications, such as valve replacement, endomyocardectomy or thrombectomy. Evidence of hypersplenism and pain due to splenic infarction are indications for splenectomy (Gotlib, 2015).

Prognosis

CEL-NOS is a clinically aggressive disease, with a high rate transformation to acute leukemia, resistant to conventional therapy, and short survival. In a small series of 10 patients with CEL-NOS, the median survival time was little over 22 months with 50% of patients transformed to acute leukemia (Helbig et al 2012). Splenomegaly, increased blasts in bone marrow, cytogenetic abnormalities and dysplastic features of myeloid lineage are unfavorable prognostic findings. However, idiopathic HES is more heterogeneous and the median survival is longer than that of CEL-NOS (Wang et al, 2016). Features that signify a better prognosis include the absence of cardiac or neurologic involvement, lower eosinophil counts, and steroid-responsiveness.

Genetics

Note

Mutations in the JAK2, ASXL1, TET2, and EZH2 genes are frequently seen in CEL-NOS cases. Recently, Anderson and colleagues isolated eosinophils and performed next generation whole genome sequencing in five patients with idiopathic HES. Somatic missense mutations were found in three patients, including spliceosome gene PUF60 and the cadherin gene CDH17. In addition, they showed that aberrant DNA methylation patterns can distinguish clonal from reactive eosinophilia, which may be very useful in daily clinical work (Andersen et al, 2015). Other study used targeted next-generation sequencing panels designed for myeloid neoplasms to bone marrow specimens from a cohort of 51 idiopathic HES patients and 17 CEL-NOS

patients (Wang et al, 2016). Mutations were detected in 14/51 (28%) of idiopathic HES involving single gene in 7 and ≥ 2 in the other 7 patients. Mutations frequently affected genes involving DNA methylation and chromatin modification. The more frequently mutated genes included ASXL1, TET2, EZH2, SETBP1, CBL, and NOTCH1. Mutations that characterize classic myeloproliferative neoplasms, including JAK2 V617F, MPL, and CALR, were all negative. KIT mutations were also not detected in any of their cases. The other 17 CEL-NOS showed multiple mutations, involving ASXL1, CSF3R, SETBP1, U2AF1, EZH2 and ETV6. However somatic mutations in genes such as TET2, JAK2, ASXL2, TP53 and others have been frequently found in elderly healthy individuals, therefore, these mutations should be interpreted with caution. Moreover, idiopathic HES patients with mutations, as a group, showed a number of clinical, laboratory and bone marrow findings resembling CEL-NOS. Wang and Colleagues concluded that targeted next-generation sequencing helps to establish clonality in a subset of patients with hypereosinophilia that would otherwise be classified as idiopathic hypereosinophilic syndrome (Wang et al 2016).

References

Andersen CL, Nielsen HM, Kristensen LS, Søgaard A, Vikeså J, Jønson L, Nielsen FC, Hasselbalch H, Bjerrum OW, Punj V, Grønbæk K. Whole-exome sequencing and genome-wide methylation analyses identify novel disease associated mutations and methylation patterns in idiopathic hypereosinophilic syndrome. Oncotarget. 2015 Dec 1;6(38):40588-97

Bain BJ. Eosinophilic leukemia and idiopathic hypereosinophilic syndrome are mutually exclusive diagnoses. Blood. 2004 Dec 1;104(12):3836; author reply 3836-7

Bain BJ, Gilliland DG, Horny H-P, Hasserjian RP, Orazi A. Chronic eosinophilic leukaemia, not otherwise specified. Swerdlow S, Harris NL, Stein H, Jaffe ES, Theile J, Vardiman JW, eds.

Crane MM, Chang CM, Kobayashi MG, Weller PF. Incidence of myeloproliferative hypereosinophilic syndrome in the United States and an estimate of all hypereosinophilic syndrome incidence J Allergy Clin Immunol 2010 Jul;126(1):179-81

Gotlib J. World Health Organization-defined eosinophilic disorders: 2017 update on diagnosis, risk stratification, and management Am J Hematol 2017 Nov;92(11):1243-1259

Gotlib J, Cools J. Five years since the discovery of FIP1L1-PDGFRA: what we have learned about the fusion and other molecularly defined eosinophilias Leukemia 2008 Nov;22(11):1999-2010

Helbig G, Soja A, Bartkowska-Chrobok A, Kyrcz-Krzemień S. Chronic eosinophilic leukemia-not otherwise specified has a poor prognosis with unresponsiveness to conventional treatment and high risk of acute transformation Am J Hematol 2012 Jun;87(6):643-5

Ogbogu PU, Bochner BS, Butterfield JH, Gleich GJ, Huss-Marp J, Kahn JE, Leiferman KM, Nutman TB, Pfab F, Ring J, Rothenberg ME, Roufosse F, Sajous MH, Sheikh J, Simon D, Simon HU, Stein ML, Wardlaw A, Weller PF, Klion AD. Hypereosinophilic syndrome: a multicenter, retrospective analysis of clinical characteristics and response to therapy J Allergy Clin Immunol 2009 Dec;124(6):1319-25

Tefferi A, Patnaik MM, Pardanani A. Eosinophilia: secondary, clonal and idiopathic Br J Haematol 2006 Jun;133(5):468-92

Wang SA, Tam W, Tsai AG, Arber DA, Hasserjian RP, Geyer JT, George TI, Czuchlewski DR, Foucar K, Rogers HJ, Hsi ED, Bryan Rea B, Bagg A, Dal Cin P, Zhao C, Kelley TW, Verstovsek S, Bueso-Ramos C, Orazi A. Targeted next-generation sequencing identifies a subset of idiopathic hypereosinophilic syndrome with features similar to chronic eosinophilic leukemia, not otherwise specified Mod Pathol 2016 Aug;29(8):854-64

This article should be referenced as such:

Mohamed AN. Chronic Eosinophilic Leukemia-Not Otherwise Specified (CEL-NOS) - Idiopathic Hypereosinophilic Syndrome (IHES). Atlas Genet Cytogenet Oncol Haematol. 2019; 23(3):72-75.