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Hypereosinophilic syndrome

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Eosinophilia

Eosinophilia is commonly defined as an elevated percentage of eosinophils, with an absolute eosinophil count > 500 cells per cubic millimeter

Secondary

Primary : 1) Idiopathic

2) Clonal

secondary eosinophilia

- **parasite infections:** (tissue-invasive helminths)
- **Allergic conditions**
- **vasculitides**
- **Drugs**(allopurinol, carbamazepine, antibiotics,....
- **Eosinophilic lung disease**
- **Malignancy** : Hodgkin,NHL,ALL,LCH, solid tumors

TABLE- World Health Organization Classification of Myeloid Malignancies

" Myeloproliferative neoplasms"

- Chronic myelogenous leukemia, *BCR-ABL1 positive*
- Chronic neutrophilic leukemia
- Polycythemia vera
- Primary myelofibrosis
- Essential thrombocythemia
- Chronic eosinophilic leukemia, not otherwise specified
- Mastocytosis
- Myeloproliferative neoplasms, unclassifiable

Primary eosinophilia

"**clonal eosinophilia** " is based on the presence or of either a molecular , cytogenetic or bone marrow histological evidence for a myeloid neoplasm

"**idiopathic eosinophilia** " is based on the absence of either a molecular, cytogenetic or bone marrow histological evidence for a myeloid neoplasm

Hypereosinophilic Syndrome and Clonal Eosinophilia:Point-of-Care Diagnostic Algorithm and Treatment Update

Mayo Clin Proc. • February 2010;85(2):158-164

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- In 1968 Hardy and Anderson coined the term " hypereosinophilic syndrome" to describe patients with prolonged eosinophilia of unknown cause.

- "*Hypereosinophilia*" simply means an absolute eosinophil count of > (1500/mm3)

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In 1975 Chusid et al used 3 diagnostic criteria for HES

(1) persistent eosinophilia of > 1500/mm3 for longer than 6 months;

(2) lack of evidence for parasitic, allergic, or other known causes of eosinophilia;

(3) signs and symptoms of organ involvement.

Idiopathic eosinophilia

Idiopathic eosinophilia implies that both secondary and clonal eosinophilia have been ruled out as possible diagnoses

A subcategory of idiopathic eosinophilia

"Hypereosinophilic syndrome"

(1) persistent eosinophilia of > (1500/mm3) for longer than 6 mo

(1) lack of evidence for parasitic, allergic, or other known causes of eosinophilia;

(3) signs and symptoms of organ involvement.

Clonal eosinophilia

Clonal eosinophilia represents neoplastic proliferation of eosinophils as part of an underlying stem cell–derived myeloid malignancy

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World Health Organization (WHO) classification of clonal Eosinophilia

- Myeloid/lymphoid neoplasms with eosinophilia and mutations involving (PDGFR) α/β or fibroblast growth factor receptor 1 (FGFR-1)
- Chronic eosinophilic leukemia, not otherwise specified (CEL-NOS)
- Clonal eosinophilia might also accompany other WHO–defined myeloid malignancies

WHO classification

Myeloid and lymphoid neoplasms associated with "*eosinophilia*"

- Myeloid and lymphoid neoplasms associated with *PDGFRA* rearrangement
- Myeloid neoplasms associated with *PDGFRB rearrangement*
- Myeloid and lymphoid neoplasms associated with *FGFR1 abnormalities*

TABLE II. 2008 World Health Organization Classification of Eosinophilic Disorders

Myeloid and lymphoid neoplasms with eosinophilia and abnormalities of *PDGFRA*, *PDGFRB*, or *FGFR1*

Diagnostic criteria of an MPN[a] with eosinophilia associated with *FIP1L1-PDGFRA*

A myeloproliferative neoplasm with prominent eosinophilia

And

Presence of a *FIP1L1-PDGFRA* fusion gene[b]

Diagnostic criteria of MPN associated with *ETV6-PDGFRB* fusion gene or other rearrangement of *PDGFRB*

A myeloproliferative neoplasm, often with prominent eosinophilia and sometimes with neutrophilia or monocytosis

And

Presence of t(5;12)(q31~q33;p12) or a variant translocation[c] or, demonstration of an *ETV6-PDGFRB* fusion gene or rearrangement of PDGFRB

Diagnostic criteria of MPN or acute leukemia associated with *FGFR1* rearrangement

A myeloproliferative neoplasm with prominent eosinophilia and sometimes with neutrophilia or monocytosis

OR

Acute myeloid leukemia or precursor T-cell or precursor B-cell lymphoblastic leukemia/lymphoma (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

Chronic Eosinophilic Leukemia, not otherwise specified (NOS)

1. There is eosinophilia (eosinophil count $>1.5x10^9$/L)
2. There is no Ph chromosome or *BCR-ABL* fusion gene or other myeloproliferative neoplasms (PV, ET, PMF, systemic mastocytosis) or MDS/MPN (CMML or atypical CML)
3. There is no t(5;12)(q31~q35;p13) or other rearrangement of *PDGFRB*
4. There is no *FIP1L1-PDGFRA* fusion gene or other rearrangement of *PDGFRA*
5. There is no rearrangement of *FGFR1*
6. The blast cell count in the peripheral blood and bone marrow is less than 20% and there is no inv(16)(p13q22) or t(16;16)(p13;q22) or other feature diagnostic of AML
7. There is a clonal cytogenetic or molecular genetic abnormality, or blast cells are more than 2% in the peripheral blood or more than 5% in the bone marrow.

Idiopathic Hypereosinophilic Syndrome (HES)

Exclusion of the following:

1. Reactive eosinophilia
2. Lymphocyte-variant hypereosinophilia (cytokine-producing, immunophenotypically-aberrant T-cell population)
3. Chronic eosinophilic leukemia, NOS
4. WHO-defined myeloid malignancies associated eosinophilia (e.g. MDS, MPNs, MDS/MPNs, or AML)
5. Eosinophilia-associated MPNs or AML/ALL with rearrangements of *PDGFRA*, *PDGFRB*, or *FGR1*.
6. The absolute eosinophil count of $>1,500/mm^3$ must persist for at least 6 months and tissue damage must be present. If there is no tissue damage, idiopathic hyerpeosinophilia is the preferred diagnosis.

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2008 World Health Organization Classification of Eosinophilic Disorders

1) Myeloid and lymphoid neoplasms with eosinophilia and abnormalities of PDGFRA, PDGFRB, or FGFR1

2) Chronic Eosinophilic Leukemia, not otherwise specified (NOS)

3) Idiopathic Hypereosinophilic Syndrome (HES)

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Myeloid and lymphoid neoplasms with eosinophilia and abnormalities of PDGFRA, PDGFRB, or FGFR1

- Diagnostic criteria of an MPN with eosinophilia associated with FIP1L1-PDGFR
- Diagnostic criteria of MPN associated with ETV6-PDGFRB fusion gene : Presence of t(5;12)(q31q33;p12) or a variant translocationc
- Diagnostic criteria of MPN or acute leukemia associated with FGFR1 rearrangement
- Acute myeloid leukemia or precursor T-cell or precursor B-cell lymphoblastic leukemia/lymphoma (usually associated with peripheral blood or bone marrow eosinophilia) AND Presence of t(8;13)(p11;q12) or a variant translocation

Chronic Eosinophilic Leukemia, not otherwise specified (NOS)

- 1. There is eosinophilia
- 2. There is no Ph chromosome or BCR-ABL fusion gene or other myeloproliferative neoplasms (PV, ET, PMF, systemic mastocytosis) or MDS/MPN (CMML or atypical CML)
- 3. There is no t(5;12)(q31q35;p13) or other rearrangement of PDGFRB, no FIP1L1-PDGFRA fusion gene or other rearrangement of PDGFR, no rearrangement of FGFR1
- 4. The blast cell count in the peripheral blood and bone marrow is less than 20% and there is no inv(16)(p13q22) or t(16;16)(p13;q22) or other feature diagnostic of AML
- 5.There is a clonal cytogenetic or molecular genetic abnormality, or blast cells are more than 2% in the peripheral blood or more than 5% in the bone marrow.

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Idiopathic Hypereosinophilic Syndrome

EXCLUSION OF

- 1. Reactive eosinophilia
- 2. Lymphocyte-variant hypereosinophilia (aberrant T-cell population)
- 3. Chronic eosinophilic leukemia
- 4. WHO-defined myeloid malignancies associated eosinophilia (e.g. MDS, MPNs, MDS/MPNs, or AML)
- 5. Eosinophilia-associated with rearrangements of PDGFRA, PDGFRB, or FGR1.
- 6. The absolute eosinophil count of >1,500/mm3 must persist for at least 6 months and tissue damage must be present.

Diagnostic algorithm for clonal or idiopathic eosinophilia

When evaluating a patient with eosinophilia that is not thought to be secondary, 5 diagnostic possibilities

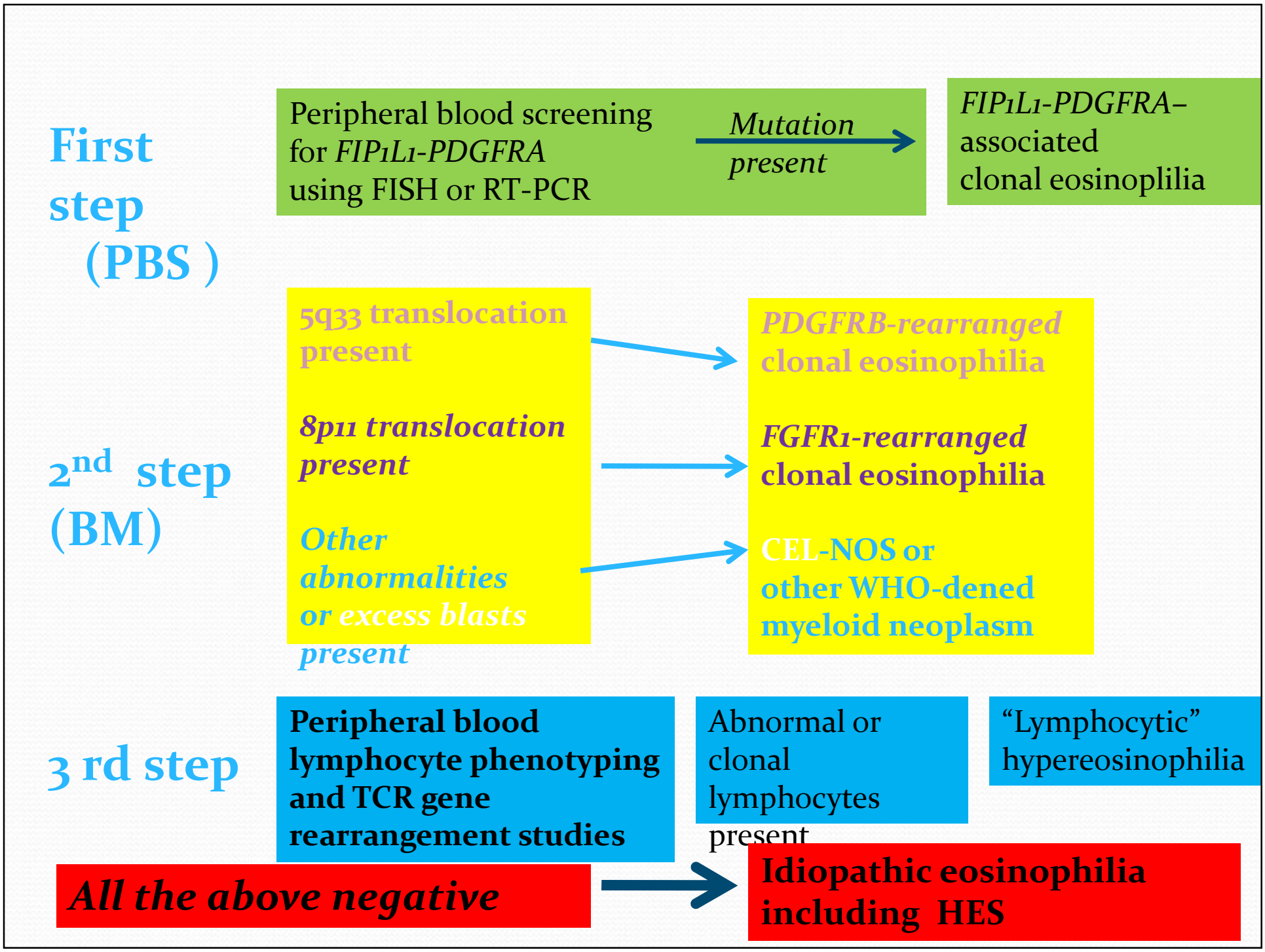
(1) Myeloid or lymphoid neoplasms associated with eosinophilia and *PDGFR A/B or FGR1 rearrangements*

(2) Clonal eosinophilia associated with an otherwise WHO-defined myeloid malignancy (CML, systemic mastocytosis, MML)

(3) CEL-NOS

(4)Lymphocytic variant hypereosinophilia, and

(5) Idiopathic eosinophilia including HES


First step (PBS)
Peripheral blood screening for FIP1L1-PDGFRA using FISH or RT-PCR
Mutation present
FIP1L1-PDGFRA–associated clonal eosinoplilia
2nd step (BM)
5q33 translocation present
8p11 translocation present
Other abnormalities or excess blasts present
PDGFRB-rearranged clonal eosinophilia
FGFR1-rearranged clonal eosinophilia
CEL-NOS or other WHO-dened myeloid neoplasm
3 rd step
Peripheral blood lymphocyte phenotyping and TCR gene rearrangement studies
Abnormal or clonal lymphocytes present
"Lymphocytic" hypereosinophilia
All the above negative
Idiopathic eosinophilia including HES

Bone marrow biopsy, tryptase stain, T cell clonality study
&
cytogenetic studies and FISH or RT-PCR for *FIP1L1-PDGFRA*

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FIP1L1-PDGFRA positive or 4q-

↓

PDGFRA rearranged myeloid neoplasm with eosinophili

5q33 translocation

↓

PDGFRB rearranged myeloid neoplasm With eosinophili

8p11 translocation

↓

FGFR1 rearranged myeloid neoplasm With eosinophili

BM histology shows abnormalities other than eosinophilia

↓

Use histology to make specific diagnosis

BM histology Only eosinophilia & No clonal T cells

↓

PB blast > 2% or BM blast > 5% or Abnormal cytogenetics

Yes

↓

CEL
HES

No

↓

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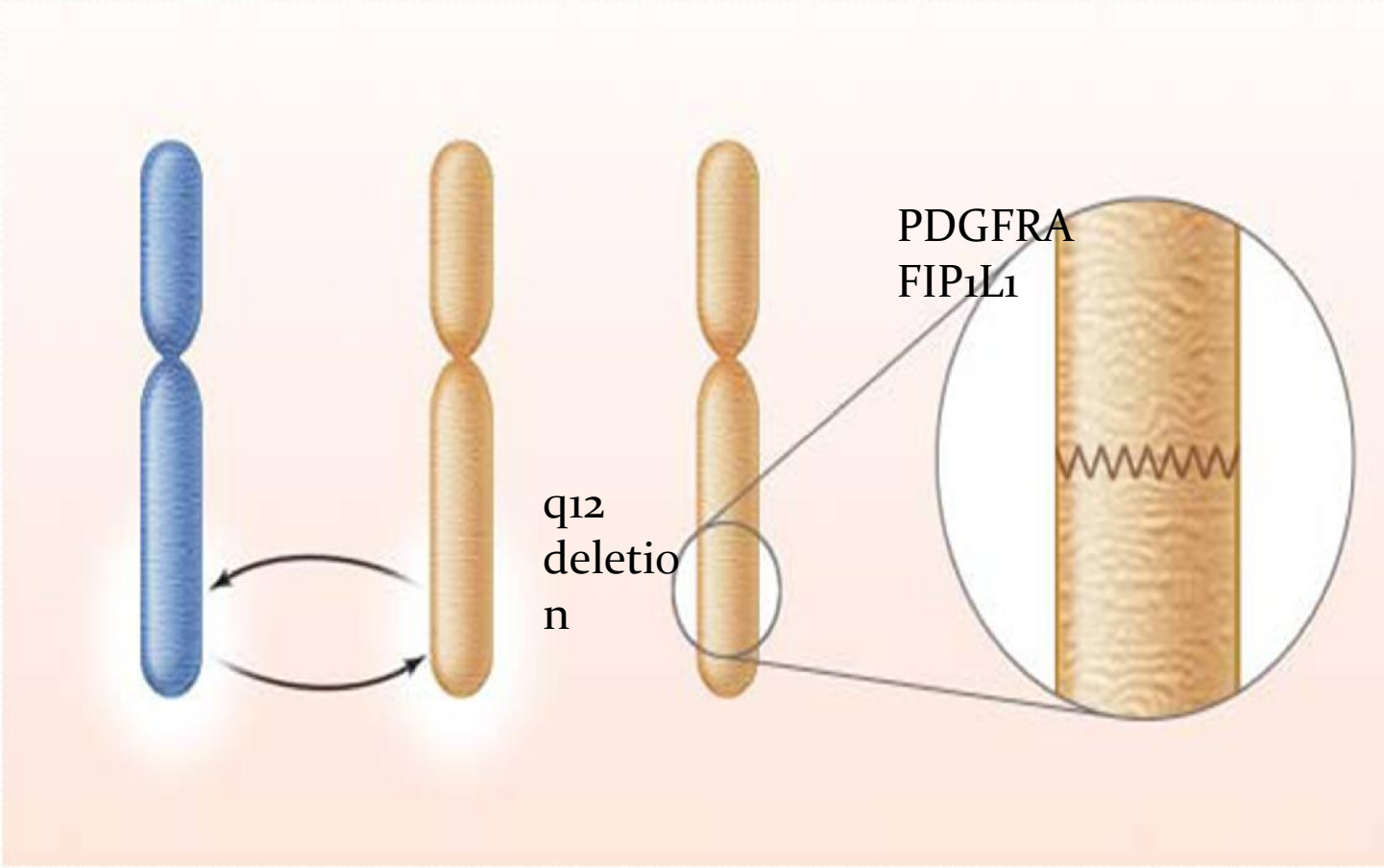

The FIP1L1-PDGFR fusion tyrosine kinase in hypereosinophilic syndrome and chronic eosinophilic leukemia: implications for diagnosis, classification, and management

Idiopathic hypereosinophilic syndrome(HES) and chronic eosinophilic leukemia (CEL) comprise a spectrum of indolent to aggressive diseases characterized by unexplained, persistent hypereosinophilia

Recent reports indicate that HES and CEL are imatinib-responsive malignancies, with rapid and complete hematologic remissions

BLOOD, 15 APRIL 2004 VOLUME 103, NUMBER 8

Definition of HES

HES was defined by Chusid et al (1975) who proposed three

Diagnostic criteria:

1) Persistent eosinophilia of >1500 /mm3 for > 6 months associated with signs and symptoms of hypereosinophilic disease.

2) Lack of evidence for parasitic, allergic or other known causes

3) signs and symptoms of organ involvement, hepatos plenomegaly, congestive heart failure, diffuse or focal nervous system abnormalities, pulmonary fibrosis, fever, weight loss and anaemia.

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Curr Opin Hematol. 2009 Jan;16(1):3-8.
Advances in diagnosis and treatment of eosinophilia

Subtypes of HES

- Myeloproliferative variants of HES : myeloproliferative-HES patients may have interstitial deletions on chromosome 4q12 that lead to fusion of the FIP1-like 1 /PDGFRA genes
- Lymphocytic-variant of HES : a primary lymphoid disorder characterized by nonmalignant expansion of a T-cell population able to produce eosinophilopoietic cytokines, T-cell population being identified by flow cytometry or reverse transcriptase-PCR for T-cell receptor usage or both.

- ***The distinction between clonal and idiopathic eosinophilia is arbitrary, and evidence suggests that HES may represent an underlying myeloid neoplasm !!!***

- ***Patients with FIP1L1-PDGFRA–positive clonal eosinophilia were before diagnosed as having HES***

The lymphocytic HES variant

- Identification of lymphocytic variant of the hypereosinophilic syndrome rests upon recognition of **distinct helper T cell subsets (TH1 and TH2)** and clonal overgrowth of specific cells.
- IL-5 production by T cells from HES patients established the importance of the TH2 cell in pathophysiology and identification of a HES patient with a CD3-CD4+ T cell subset producing IL-4 and IL-5

The lymphocytic HES variant

The most prevalent T cell clone associated with lymphocytic HES appears to be the CD3- CD4+ clone

These clones generally produce the TH2 cytokines IL-4 and IL-13, in addition to IL-5, and patients harbouring the clones often have markedly elevated serum immunoglobulin E

Decreased T cell receptor (TCR)-CD3 expression appears to be related to reduced CD3c expression

Clinical features of lymphocytic HES

- In contrast to myeloid HES, lymphocytic HES affects males

  and females equally
- Patients with lymphocytic HES often show predominant cutaneous manifestations, including pruritus, eczema, erythroderma, urticaria and angioedema.
- In general, patients with lymphocytic HES do not show the predilection to developing cardiac disease as is common in myeloproliferative HES

stepwise approach to specific diagnosis

- Careful assessment of the peripheral blood smear,
- Bone marrow morphologic features, cytogenetic analysis,
- Molecular studies : screening for *FIP1L1-PDGFRA, and peripheral blood* lymphocyte phenotyping and T-cell receptor gene rearrangement (TCR)

Cytogenetic of BM

PDGFRB (5q33 translocations)
FGFR1 (8p11.2 translocations)
PDGFRA (4q12 translocations)

FIP1L1-PDGFRA is karyotypically occult **and requires FISH or RT-PCR studies for detection**

Asymptomatic Patient with clonal eosinophilia

- **In the absence of symptoms, the best approach is to postpone treatment until the diagnostic work-up is completed and the specific diagnosis made**

- **In clonal eosinophilia associated with imatinib mesylate–sensitive molecular markers(eg, *FIP1L1-PDGFRA, PDGFRB rearrangement, BCRABL),* early initiation of therapy is reasonable because**

(1)development of symptoms or evolution into aggressive disease is inevitable

(2) targeted therapy results in complete clinical and molecular remission and can prevent complications, including leukemic transformation.

Asymptomatic Patient with eosinophilia

- Our personal preference, is to avoid drug therapy in asymptomatic patients with idiopathic eosinophilia

- unless the absolute eosinophil count is too high (eg, >30,000)
- Even then, an individualized approach is recommended

Hypereosinophilic Syndrome and Clonal Eosinophilia:Point-of-Care Diagnostic Algorithm and Treatment Update, *Mayo Clin Proc.* • *February 2010;85(2):158-164*

Common Features of FIP1L1-PDGFRA - associated myeloproliferative neoplasm

- Clinical : Marked male predominance , Adult presentation
- Peripheral blood/bone marrow: Moderate to severe peripheral eosinophilia, mildly to moderately elevated serum **tryptase**
- Marrow eosinophilia
- Genotypic Findings: FIP1L1-PDGFRA demonstrated by FISH or RT-PCR
- Normal karyotype

Treatment of clonal eosinophilia

FIP1L1-PDGFRA pos+

- The first drug in clonal eosinophilia is **imatinib mesylate**,but only in the presence of *FIP1L1-PDGFRA or PDGFRA/PDGFRB translocations*
- Evidence supports the use of low-dose imatinib mesylate (100 mg/d) for inducing molecular and histologic remission in *FIP1L1-PDGFRA–positive clonal eosinophilia*
- Lower doses (100 mg/wk) might be effective for remission maintenance.

- In patients with imatinib mesylate–resistant *FIP1L1-PDGFRA–positive clonal eosinophilia,* it is reasonable to switch to **interferon alfa** therapy first.

- If such treatment fails, mutation information should be obtained (available only in research laboratories at this time), and

- In the presence of the T674I mutation, **Nilotinib or sorafenib** therapy should be initiated

Treatment of clonal eosinophilia
PDGFRB mutations

Imatinib therapy is also effective for clonal eosinophilia associated with *PDGFRB mutations*(5q31-33 cytogenetic abnormalities)

Drug doses in this instance have usually been higher (400 mg/d)

As with *FIP1L1-PDGFRA*– positive clonal eosinophilia, patients with *PDGFRB*,might achieve clinical and cytogenetic remissions with interferon alfa therapy

The presence of 5q33 or 4q12 translocations predicts favorable response to treatment with imatinib mesylate (Gleevec)

whereas 8p11.2 translocations are associated with aggressive myeloid malignancies that are refractory to current drug therapy

FGFR1-rearranged clonal eosinophilia

Aggressive disease course (myeloproliferation with eosinophilia , LAP and a high incidence of T cell lymphoblastic lymphoma with progression to acute myeloid leukemia)

R: Early aggressive combination chemotherapy (eg, Hyper-CVAD [fractionated cyclophosphamide,vincristine, Adriamycin and dexamethasone]) followed by ASCT

Management of HES

Corticosteroids are the cornerstone of therapy for HES, Treatment with oral prednisone is usually started at 1 mg/kg/d and continued for 1 to 2 weeks before the dose is tapered slowly during the ensuing 2 to 3 months.

If symptoms recur with a prednisone dosage level of greater than 10mg/d :

Hydroxyurea :(starting dosage, 500 mg twice daily) **or**

Interferon alfa :(starting dosage, 1 million units/3 ×/w

Management of HES

- Tissue injury in patients with HES is mediated by material released from eosinophilic granules,
- Such eosinophil-derived substances,could conceivably contribute to thromboembolic complications associated with HES.
- The major goal of therapy for symptomatic HES is to debulk the blood and tissue eosinophil burden.

Management of HES

For patients in whom usual therapy fails several cytotoxic (eg, cladribine) and noncytotoxic (eg, cyclosporine) drugs have been used as salvage therapy,

Newer Recommended drugs:

Imatinib mesylate
Mepolizumab (Anti Interleukin 5)
Alemtuzumab (targets the CD52 antigen on eos)

Management of HES

- occasional reports have described successful results with imatinib mesylate therapy for *FIP1L1-PDGFRA–negative patients,usually at* higher drug dosage levels(400-800 mg/d)

- Therefore,initiation of a therapeutic trial of high-dosage (800 mg/d) imatinib mesylate for 2 to 4 weeks could be tried before alemtuzumab or mepolizumab treatment is considered in patients with refractory HES.

Mepolizumab

In a large randomized study, **intravenous mepolizumab(750 mg) was administered monthly** to corticosteroid-dependent patients with HES and resulted in successful reduction of their corticosteroid dose and lowering of blood eosinophil

However, mepolizumab-induced remissions were not durable, and relapse occurred 1 to 3 months after discontinuation of therapy.

Mepolizumab is currently available for patients with life-threatening HES that is not responding to usual therapy.

In a recently published study, 11 patients with refractory HES received intravenous alemtuzumab (5-30 mg) 1 to 3 times a week, and (91%) achieved normalization of their eosinophil count and alleviation of symptoms and sign

Response was quick (median, 2 weeks), but remission was not sustained in the absence of continued therapy

Alemtuzumab therapy for hypereosinophilic syndrome and chronic eosinophilic leukemia. *Clin Cancer Res.* *2009;15(1):368-373.*

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Finally, few case reports have shown successful treatment of HES or clonal eosinophilia, including a *FIP1L1- PDGFRA–positive case, with either conventional or reduced-* intensity conditioning allogeneic hematopoietic cell transplant.

We think that such therapy should be considered for drug-refractory HES or clonal eosinophilia

Successful non-myeloablative allogeneic transplantation for treatment of idiopathic hypereosinophilic syndrome.

Br J Haematol. 2002;119(1):131-134.

Allogeneic blood stem cell transplantation following non-myeloablative conditioning for hypereosinophilic syndrome.

Bone Marrow Transplant. 2002;29(5):457-458

Prognosis

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

Differential diagnosis

Systemic mastocytosis (the presence of aggregates of morphologically abnormal mast cells, demonstration of abnormal mast cell expression of CD25, or presence of *KITD816V*

chronic myelomonocytic leukemia (the presence of peripheral blood monocytes of more than 1 × 109/L)

CEL-NOS(peripheral blood eosinophil count is >1.5 00 and is accompanied by cytogenetic or morphologic evidence of a myeloid malignancy, or greater than 2% peripheral blood blasts or greater than 5% bone marrow blasts

Clonal eosinophilia VS HES

Both clonal eosinophilia and HES might be accompanied by eosinophil-mediated tissue injury in the form of

Cardiomyopathy,
Pneumonitis,
Dermatitis,
Sinusitis,
Central nervous system or peripheral neuropathy,
Gastrointestinal inflammation,
Thromboembolic complications, and…

clonal eosinophilia is usually associated with cytopenia and hepato splenomegaly