Myeloid/Lymphoid Neoplasms with Eosinophilia and Gene Rearrangement

Myeloid and/or lymphoid neoplasm with eosinophilia and an activated tyrosine kinase protein by fusion gene or mutation
- Eosinophilia present in all cases
- The majority cases are myeloid neoplasms, smaller numbers are lymphoid neoplasms or acute myeloid leukemia
- These diseases are sensitive to tyrosine kinase inhibitors

Myeloid/Lymphoid neoplasms with PDGFRA rearrangement
- A myeloid or lymphoid neoplasm with rearrangement of PDGFRA at 4q12
- Chronic eosinophilic leukemia, majority cases; acute myeloid leukemia or T-lymphoblastic leukemia/lymphoma, smaller numbers
- A very rare disease, male to female ratio 17:1
- Median age in the 40s
- Involves blood, bone marrow, spleen in all cases
- Symptoms associated with cytokine and humoral factor released from eosinophils: restrictive endocarditis, venous and arterial thrombosis, restrictive lung disease etc

Morphology: Peripheral blood with increased mature eosinophils
- Bone marrow with marked increase of eosinophils
- Tissue with infiltrate of eosinophils; Charcot-Leyden crystals may be present
- Mast cells are usually increased

Coexisting eosinophilia in cases of AML/ALL

Phenotype: Increased eosinophils with mostly normal phenotype. Small number of cases have CD23 or CD25 expression on eosinophils

Genetics: FIP1L1-PDGFRA in majority cases (resulting in cryptic deletion of 4q12; normal karyotype, but can be detected by FISH [CHIP2 probe]). Other rare 4q12 translocations include t(1;4)(q44;q12), t(4;10)(q12;p11)

Prognosis: Sensitive to tyrosine kinase inhibitors. Prognosis favorable if no organ damages

Differential: Chronic eosinophilic leukemia, NOS, hypereosinophilic syndrome

Myeloid/Lymphoid neoplasms with PDGFRB rearrangement
- A myeloid neoplasm associated with rearrangement of PDGFRB at 5q32
- Chronic myelomonocytic leukemia most common, others include, nearly all have eosinophilia
- A very rare disease, male to female ratio 2:1
- Symptoms associated with cytokine and humoral factor released from eosinophils: heart failure, organ damages
- Most cases presented as chronic myelomonocytic leukemia, various types of other myeloid neoplasms in remaining cases

Morphology: Peripheral blood with increased neutrophils (and precursors), eosinophils, monocytes
- Bone marrow with increase of neutrophils and eosinophils, and precursors
- Mast cells are usually increased

Phenotype: Increased eosinophils with mostly normal phenotype, monocytes may have aberrant phenotype
**Genetics:** t(5;12)(q32;p13.2) ETV6-PDGFB most common, more than 20 other rare translocations involving 5q32  
**Prognosis:** Sensitive to tyrosine kinase inhibitors. Prognosis favorable if no organ damages  
**Differential:** Ph-like (with PDGFRB rearrangement) B-lymphoblastic leukemia/lymphoma

<table>
<thead>
<tr>
<th>Myeloid/Lymphoid neoplasms with FGFR1 rearrangement</th>
</tr>
</thead>
<tbody>
<tr>
<td>A myeloid or lymphoid neoplasm associated with rearrangement of FGFR1 at 8p11</td>
</tr>
<tr>
<td>Heterogeneous diseases, including acute and chronic myeloid leukemia, T- and B-lymphoblastic leukemia, etc, nearly all have eosinophilia</td>
</tr>
<tr>
<td>A very rare disease, male to female ratio 1.5:1, median age 32 years</td>
</tr>
<tr>
<td>Symptoms associated with cytokine release: fever, weight loss, night sweat</td>
</tr>
<tr>
<td><strong>Morphology:</strong> Various morphology depending on types of neoplasms</td>
</tr>
<tr>
<td><strong>Phenotype:</strong> Phenotype of the corresponding neoplasms. Increased eosinophils with mostly normal phenotype</td>
</tr>
<tr>
<td><strong>Genetics:</strong> t(8;13)(p11.2;q12) ZMYM2-FGFR1 most common, more than 10 other rare translocations involving 8p11</td>
</tr>
<tr>
<td><strong>Prognosis:</strong> Poor due to high incidence of transformation. No established TKI treatment</td>
</tr>
<tr>
<td><strong>Differential:</strong> Myeloid and lymphoid neoplasm without FGFR1 rearrangement</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Myeloid/Lymphoid neoplasms with PCM1-JAK2 rearrangement</th>
</tr>
</thead>
<tbody>
<tr>
<td>A myeloid or lymphoid neoplasm associated with PCM1-JAK2 rearrangement t(8;9)</td>
</tr>
<tr>
<td>Heterogeneous diseases, including acute and chronic myeloid leukemia, T- and B-lymphoblastic leukemia, etc, nearly all have eosinophilia</td>
</tr>
<tr>
<td>A very rare disease, male to female ratio 27:1, median age 47 years</td>
</tr>
<tr>
<td>Hepatosplenomegaly common</td>
</tr>
<tr>
<td><strong>Morphology:</strong> Various morphology depending on types of neoplasms</td>
</tr>
<tr>
<td><strong>Phenotype:</strong> Phenotype of the corresponding neoplasms. Increased eosinophils with mostly normal phenotype</td>
</tr>
<tr>
<td><strong>Genetics:</strong> t(8;9)(p22;p24.1) PCM1-JAK2 most common, other rare cases include ETV6-JAK2 and BCR-JAK2</td>
</tr>
<tr>
<td><strong>Prognosis:</strong> Variable. No established TKI treatment</td>
</tr>
<tr>
<td><strong>Differential:</strong> Myeloid and lymphoid neoplasm without JAK2 rearrangement</td>
</tr>
</tbody>
</table>

**Chronic Eosinophilic Leukemia, NOS and Idiopathic Hypereosinophilic Syndrome**

Persistent eosinophilia in blood and bone marrow, with eosinophilia being the dominant abnormality, with evidence of organ damage

**Chronic eosinophilic leukemia, not otherwise specified**

A myeloproliferative disorder with clonal proliferation of eosinophils  
A very rare disease, more common in men, affect primarily elderly  
Multisystem disease affecting blood, bone marrow, spleen, and variably other organs (heart, lung, CNS, skin, GI)  
Constitutional symptoms: fever, weight loss, night sweat, fatigue, cough, angioedema, muscle pain, pruritus, diarrhea  
Endocardial fibrosis resulting restrictive cardiomyopathy, valvular regurgitation, and intracardiac thrombi, peripheral neuropathy and CNS dysfunction, lung infiltrate, rheumatologic diseases  
**Morphology:** Blood: Prominent peripheral eosinophilia, with mainly mature eosinophils. Eosinophil dysplasia may be present including uneven and sparse granulation, cytoplasmic
vacuoles, hypersegmented or hyposegmented nuclei. These changes are not specific. Blasts <20%

Bone marrow: Hypercellular, prominent eosinophil infiltrate, normal maturation, blasts <20%

Tissue: Eosinophil infiltrate, often with accompanying fibrosis

**Phenotype:** Increased eosinophils with mostly normal phenotype

**Genetics:** Cytogenetic and molecular genetic abnormalities are common. No specific genetic abnormalities

**Diagnosis:** Diagnostic criteria summarized below

<table>
<thead>
<tr>
<th>Diagnostic criteria of chronic eosinophilic leukemia, NOS (must meet all 5 criteria)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Eosinophilia (&gt;1.5 x 10⁹/L)</td>
</tr>
<tr>
<td>2. Other established myeloproliferative neoplasms excluded</td>
</tr>
<tr>
<td>3. Myeloid/lymphoid neoplasms with eosinophilia and gene rearrangement excluded</td>
</tr>
<tr>
<td>4. Less than 20% blasts in blood and bone marrow, no CBFB-MYH11 or RUNX1-RUNX1T1 rearrangements</td>
</tr>
<tr>
<td>5. Clonal cytogenetic abnormality or clonal molecular genetic abnormality or blasts &gt;2% in blood or blasts &gt;5% in bone marrow</td>
</tr>
</tbody>
</table>

**Prognosis:** Generally poor, median survival 2 years.

**Differential:** Other chronic or acute leukemia of myeloid or lymphoid neoplasms with eosinophilia

**Idiopathic hypereosinophilic syndrome**

Sustained eosinophilia with evidence of organ infiltration with unknown etiology

Affect more commonly in younger population

Evidence of organ damage includes cardiomyopathy, pulmonary disease, renal disease

Likely a heterogeneous group including both reactive and neoplastic eosinophilia

**Morphology:** Blood: Prominent peripheral eosinophilia, with mainly mature eosinophils.

Eosinophil dysplasia absent

Bone marrow: Hypercellular, prominent eosinophil infiltrate, normal maturation

Tissue: Eosinophil infiltrate, often with accompanying fibrosis

**Phenotype:** Increased eosinophils with mostly normal phenotype

**Genetics:** Absent cytogenetic and molecular genetic abnormalities

**Diagnosis:** Diagnostic criteria summarized below

<table>
<thead>
<tr>
<th>Diagnostic criteria of idiopathic hypereosinophilic syndrome (must meet all 4 criteria)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Eosinophilia (&gt;1.5 x 10⁹/L) greater than 6 months</td>
</tr>
<tr>
<td>2. Evidence of organ damage (heart, lung, kidney, or other organs)</td>
</tr>
<tr>
<td>3. All established myeloproliferative neoplasms and AML excluded</td>
</tr>
<tr>
<td>4. No clonal cytogenetic abnormality or clonal molecular genetic abnormality or increase of blasts in blood and bone marrow</td>
</tr>
</tbody>
</table>

**Prognosis:** Variable, depends on degree and duration of organ damage

**Differential:** Chronic or acute leukemia of myeloid or lymphoid neoplasms with eosinophilia
Mastocytosis
A heterogeneous group of diseases with proliferation of neoplastic mast cells and *KIT D816V* mutation or rarely other *KIT* mutations
Rare diseases with unknown incidence

Cutaneous mastocytosis
Proliferation of neoplastic mast cells limited to skin without systemic involvement
Mostly affect children
Three variants:
- *Urticaria pigmentosa/maculopapular cutaneous mastocytosis (UP)*: isolated lesions in skin
- *Diffuse cutaneous mastocytosis (DCM)*: diffusely thickened skin with disseminated macular or maculopapular lesions
- *Mastocytoma of skin*: Singular lesion in skin

**Morphology:** Spindle shaped mast cells infiltrate skin in clusters or sheets, may accumulate perivascular and periadnexal. Mastocytoma contains sheets of mature appearing high metachromatic mast cells

**Phenotype:** CD117+, tryptase+, CD2+ (aberrant), CD25+ (aberrant)
**Genetics:** *KIT* mutations, most common *D816V*

**Diagnosis:** Increased mast cells in skin, *KIT* mutations, serum tryptase (increased in systemic mastocytosis)

**Prognosis:** Indolent course with frequent spontaneous regression around time of puberty
**Differential:** Other cutaneous disease, systemic mastocytosis involving skin

Systemic mastocytosis
Neoplastic proliferation of mast cells in bone marrow, skin (majority cases), with or without involving other organs and tissues

**Symptoms:** Constitutional symptoms: fatigue, weight loss, fever diaphoresis
**Skin manifestation:** pruritis, urticarial, flushing, dermatographism
**Mediator-related systemic events:** abdominal pain, GI distress, syncope, hypotension etc
**Musculoskeletal symptoms:** bone pain, osteoporosis, fracture, arthralgia, myalgia

Six variants: See table below

**Morphology:** Mast cell burden in bone marrow varies depending on each variants
Aggregates of mast cells in paratrabecular and/or interstitial locations, with associated fibrosis, and often with central collection of mature lymphocytes
Mast cells spindle shaped with faintly granular cytoplasm and small oval-shaped bland nuclei

**Phenotype:** CD117+, tryptase+, CD2+ (aberrant), CD25+ (aberrant)
**Genetics:** Absent cytogenetic and molecular genetic abnormalities
**Diagnosis:** *KIT* mutations, most common *D816V*

<table>
<thead>
<tr>
<th>Six variants of systemic mastocytosis</th>
<th>Low BM mast cell burden, skin lesions present</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Indolent systemic mastocytosis</td>
<td></td>
</tr>
<tr>
<td>2. Bone marrow mastocytosis</td>
<td>Low BM mast cell burden, no skin lesions</td>
</tr>
<tr>
<td>3. Smoldering systemic mastocytosis</td>
<td>High BM mast cell burden, no features of organ damage</td>
</tr>
<tr>
<td>4. Systemic mastocytosis with an associated hematologic neoplasm</td>
<td>Coexisting systemic mastocytosis and another hematologic neoplasm in bone marrow</td>
</tr>
<tr>
<td>5. Aggressive systemic mastocytosis</td>
<td>High BM mast cell burden, with features of organ damage, usually no skin lesions</td>
</tr>
<tr>
<td>6. Mast cell leukemia</td>
<td>Very high BM mast cell burden, circulating mast cells in blood (usually &gt;10%), no skin lesions</td>
</tr>
</tbody>
</table>
**Prognosis:** Variable, depends on variant types and degree and duration of organ damage. Treatment includes histamine receptor inhibitors, proton pump inhibitors, mast cell stabilizer, tyrosine kinase inhibitors, corticosteroid, cladribine, mitostaurin, mTOR inhibitor, bone marrow transplant.

**Mast cell sarcoma**
Localized destructive growth of highly atypical mast cells
Extremely rare
Reported locations include larynx, large bowel, meninges, bone, skin
**Morphology:** Poorly differentiated, highly pleomorphic mast cells with no cytologic features of mast cells
**Phenotype:** CD117+, tryptase+, CD2+ (aberrant), CD25+ (aberrant)
**Genetics:** KIT mutations, most common D816V
**Diagnosis:** Based on confirmation of mast cell phenotype and/or KIT mutation
**Prognosis:** Aggressive, transform to mast cell leukemia in short period of time
**Differential:** Other types of lymphoma, sarcoma, and carcinoma