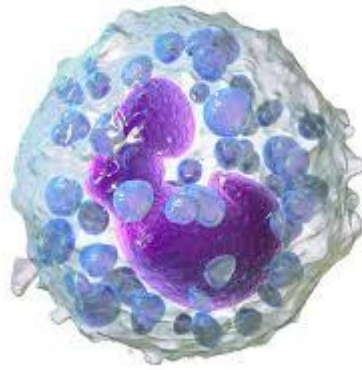


In the name of god



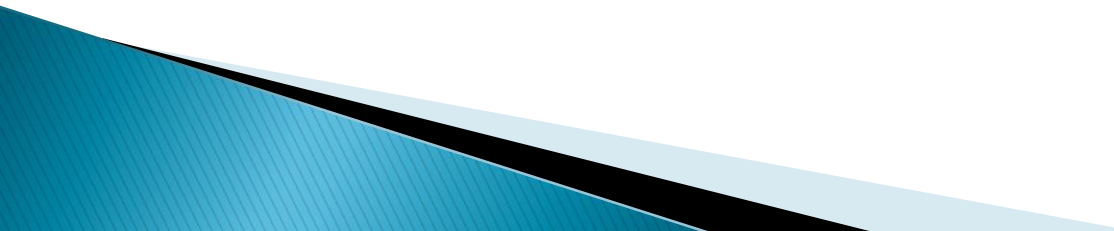


Basophil disorders

Dr.A Fathi

Pediatric Hematologist & Oncologist

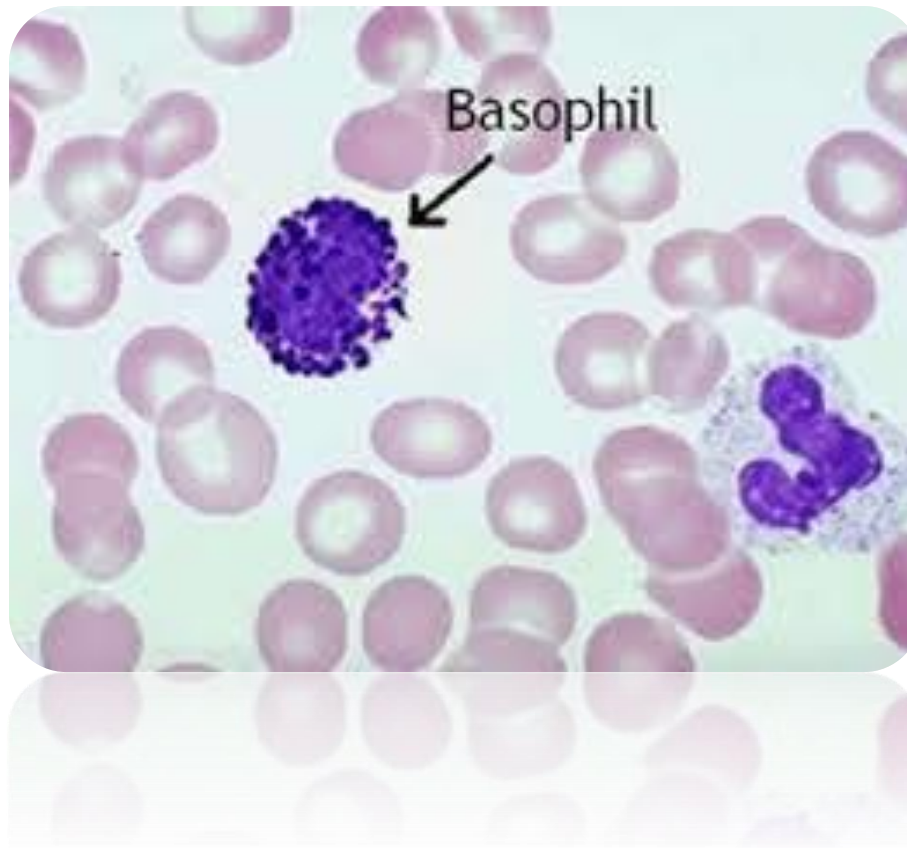
Ardebil University

- ▶ **Basophils** are one of the five white blood cell types protect your body from **infections**, **parasites**, **fungi** and **cancer cells**. Basophils drive your body's reaction to **allergens**.
 - ▶ Basophilia **may be** a sign you have an **infection**, or it may be a sign of serious medical conditions like **leukemia** or **autoimmune** disease.
- 

- ▶ A **normal** basophil count is **0.5% to 1%** of your white blood cell count.
- ▶ Basophilia is defined as an elevated absolute basophil count greater than **200 cells/uL** or relative basophil count greater than **2%**,
- ▶ The term **hyperbasophilia** refer to persistent Absolute **count > 1000 cells/ul over > 8 weeks**

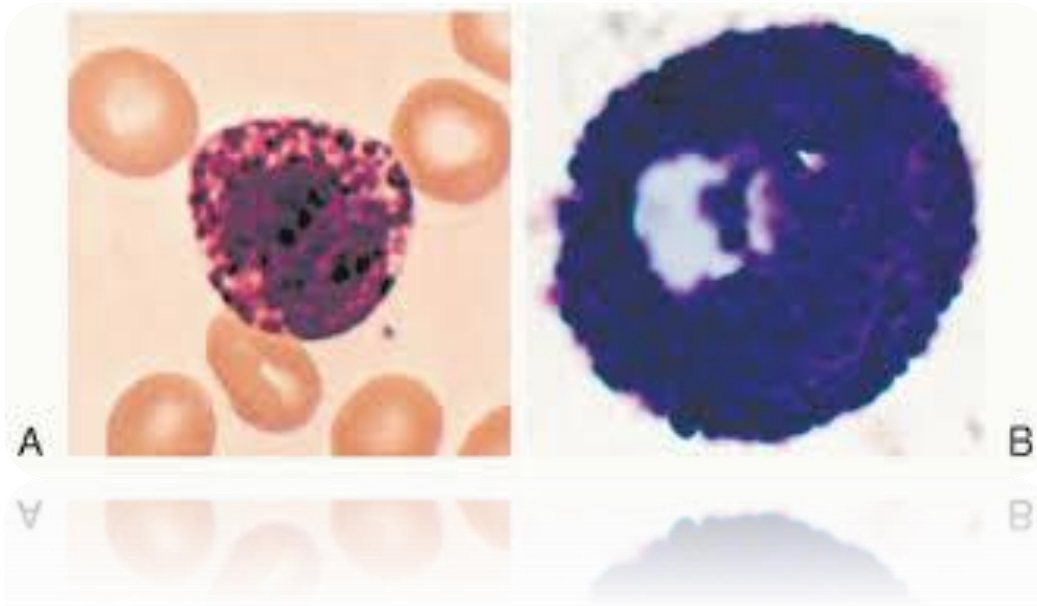
- ▶ **Manual** basophil count should be performed on **at least 400** white blood cells, **two 200–cell** differential count, to decrease bias due to statistical error.
- ▶ _ In case of **discrepant** manual and automatic count, especially if it changes the classification (**basophilia or not**), **a third 200–cell** differential count is recommended.

- ▶ Basophils have roughly the **same** size as **neutrophils**, ranging from **10 to 14 μm** . The cytoplasm generally **stains pinkish** and contains **purple-black** and coarse granules, which often obscure the cell nucleus.
- ▶ The nucleus of the basophils has a **condensed chromatin** and may be **band-shaped** or segmented into two lobes. **Nucleoli** are often **absent**



- ▶ Basophil granules may be dissolved in water during processing making their identification difficult.
- ▶ Reactive basophilia are not associated with specific dysplasia except a decrease of granularity, which is quite common.
Dysplastic basophils are usually seen in MDS and an accelerated phase of CML

- ▶ other blood cells may be **confused** with basophils: especially **neutrophils** with **toxic granulation** and **eosinophils** with abnormal **dark granules** that may be seen in some MDS and some AML (eg, AML with inv[16]).
- ▶ Finally, **mast cells** can be present in PB in an extremely rare myeloid disorder called mast cell leukemia.



Normal basophil development and function

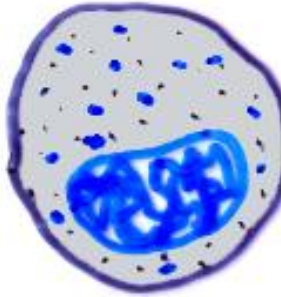
- ▶ Basophils develop along the lineage of :
 - ❖ Common myeloid progenitors
 - ❖ Granulocyte—monocyte progenitors
 - ❖ Granulocyte progenitors

- ▶ The next stage can occur in the **bone marrow** or in **spleen** as a **basophil mast** cell progenitor
- ▶ The transcription factors **CCAAT** enhancer-binding protein alpha (C/EBP alpha) and **GATA2** help directed basophil maturation and determine the fate of the cell **toward** mast cell or basophil development

- ▶ Once fully **mature basophil** migrate into the **bloodstream**
- ▶ With short **life** span survival of **2–3 days**
- ▶ Additional actions of basophil in peripheral circulation are **dependent on** several cytokines, chemokines, and other mediators
- ▶ Central to basophil activity is the cytokine **IL-3**

BASOPHILOPOEISIS

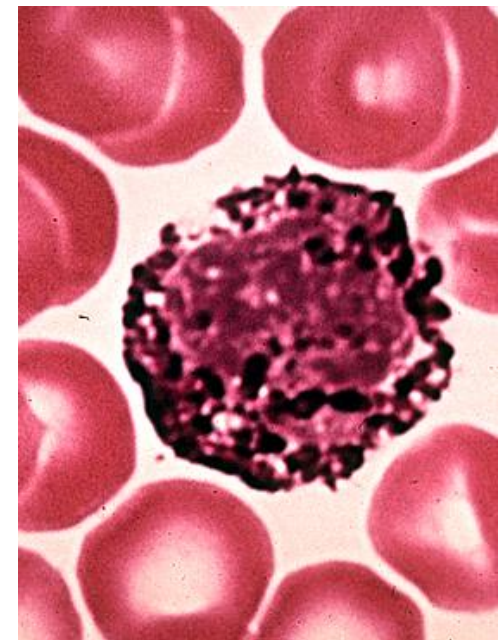
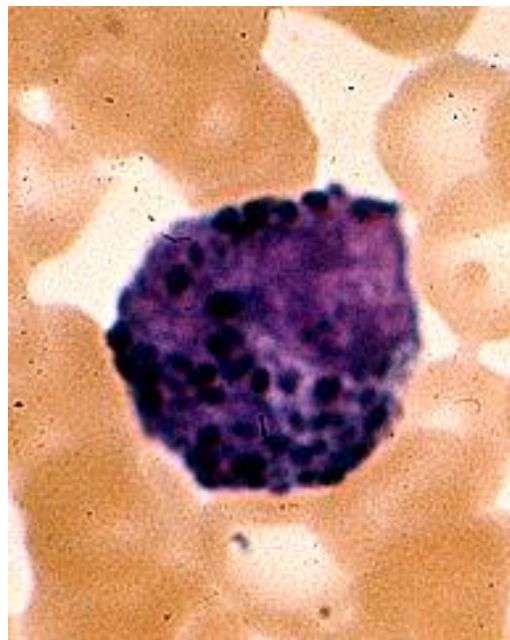
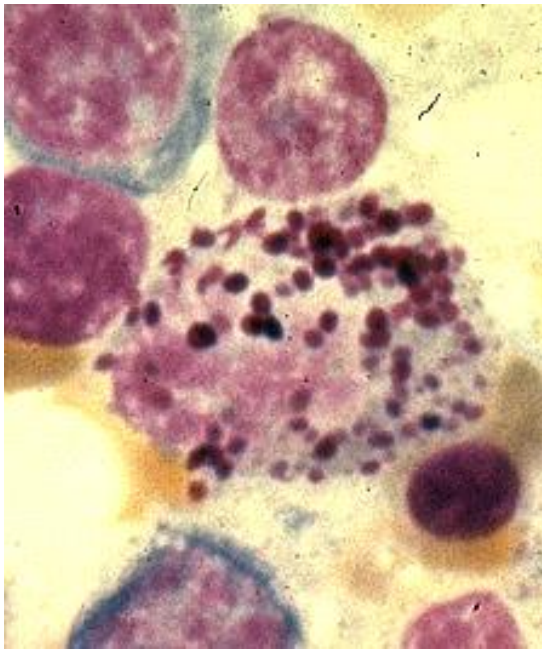
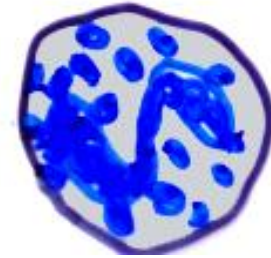
Basophilic
Myelocyte

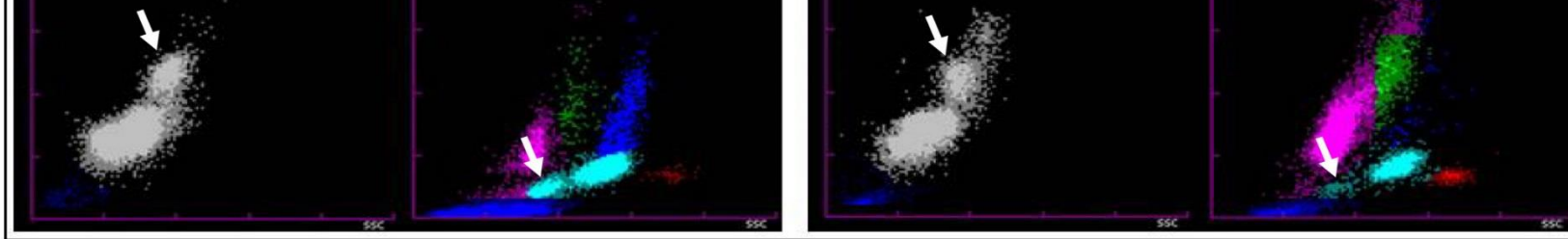


Basophilic
Metamyelocyte

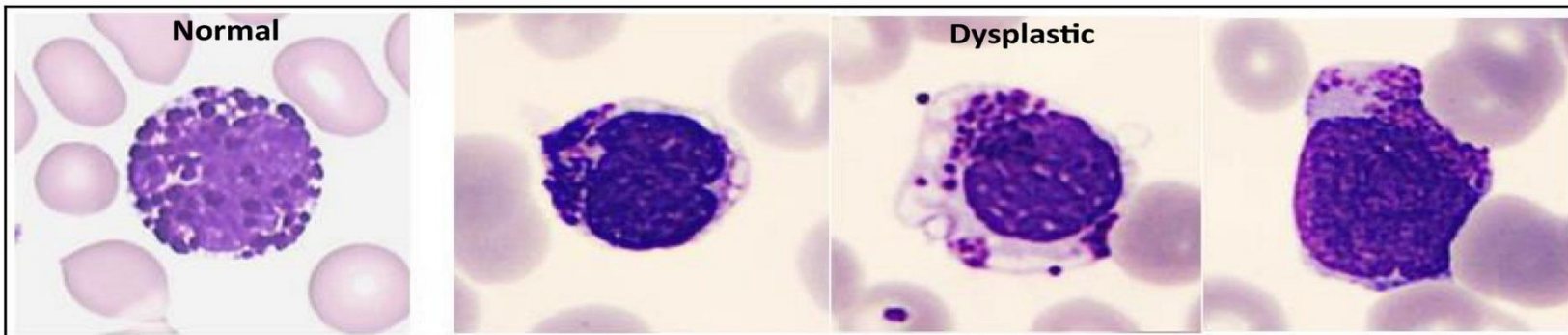


Basophil





(B) Morphology of basophils



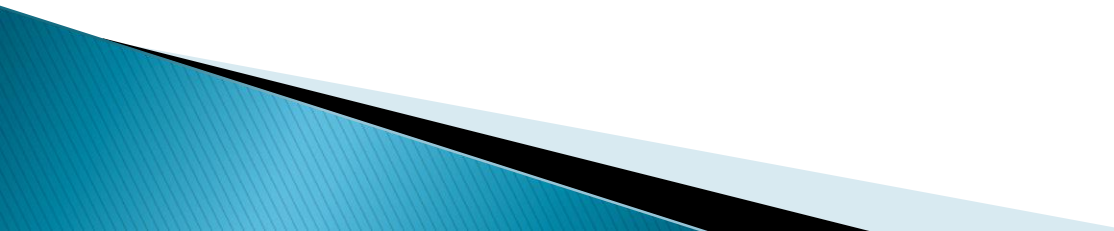
(C) Immunophenotypic profile of basophils

Ag	Basophils		Other cells			
	normal	neoplastic	pDC	Mast cell	myeloblast	neutrophil
CD203c	+	+	—	+	—	—
CD123	+	±	+	—	±	—
HLA-DR	—	±	† _{high}	† _{low}	±	—
CD34	—	—	—	—	+	—
CD117	—	—	—	+	+	—
CD38	+	±	—	† _{low}	±	—
CD33	+	±	—	† _{mod}	±	+
CD16	—	—	—	—	—	+
CD64	—	±	—	—	±	—

- ▶ A major effector role of basophil is the **rapid** release **histamine** and leukotriene upon interaction with **IgE**–antigen complex
- ▶ Basophil along with mast cells , elicit **immediate** hypersensitivity reaction in a range of **mild allergy** to life–threatening **anaphylaxis**

- ▶ Basophil also play a role in **late-phase** hypersensitivity reaction such as allergic rhinitis and asthma can occur **hourse** after encounter with an allergic trigger
- ▶ and also **delayed** hypersensitivity reaction , a process that occurs **2-3 days** after encounter with an allergen

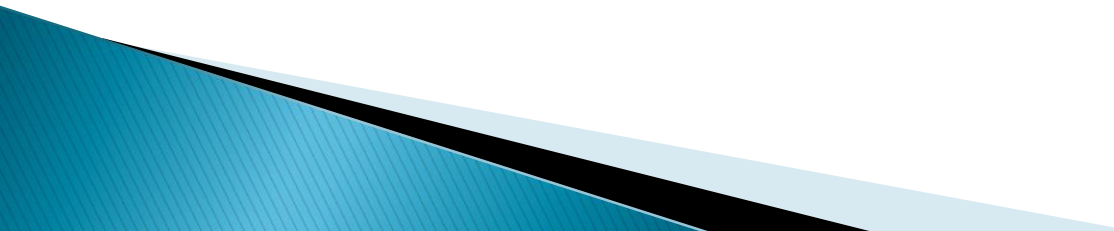
▶ **Basophilia symptoms include:**

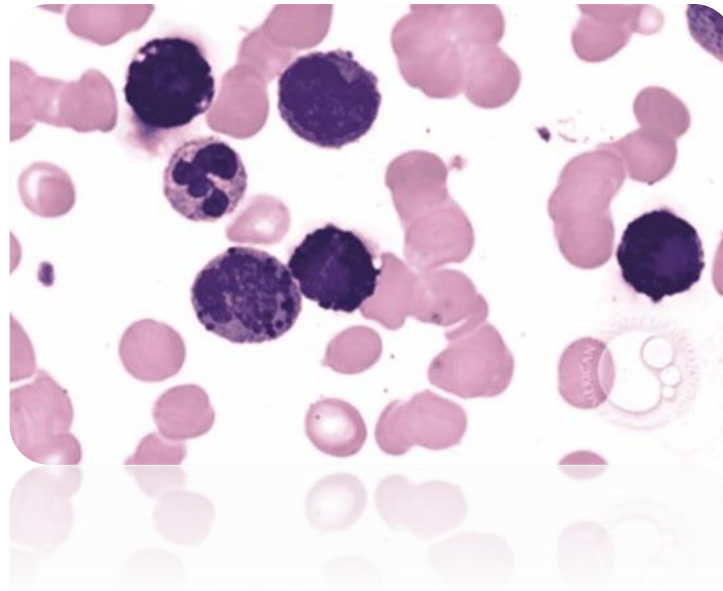
- ❖ fever
 - ❖ Feeling weak or tired.
 - ❖ Recurring or frequent infections.
 - ❖ Severe itching.
 - ❖ Skin rashes.
 - ❖ Swollen or painful joints.
- 

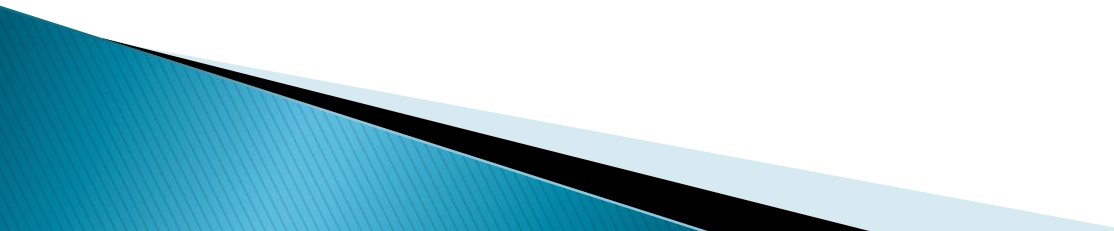
- ▶ Basophilia is a **rare** disorder
- ▶ There are three main categories when considering the cause of basophilia:
 - ▶ **The First:**
 - ❖ hematologic causes include myeloproliferative diseases
 - ▶ **The second:**
 - ❖ chronic inflammation
 - ▶ **The third:**
 - ❖ is allergic

- ▶ **First:**
- ▶ hematologic causes include myeloproliferative diseases such as :
 - ❖ AML
 - ❖ (CML) Basophil counts exceeding 30% can occur during the course of CML and heralds a poor prognosis
 - ❖ polycythemia vera,
 - ❖ primary myelofibrosis
 - ❖ essential thrombocythemia.
 - ❖ Sideroblastic anemia
 - ❖ Systemic mastocytosis
 - ❖ hypereosinophilic syndrome

- ❖ myelodysplastic syndrome.
- ❖ Striking basophilia can be seen in the very rare chronic basophilic leukemia

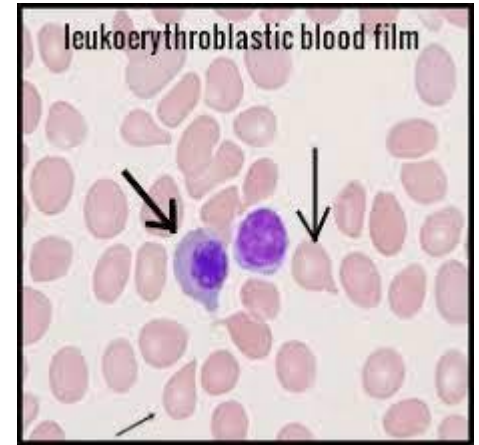
- ▶ **Acute basophilic leukemia (ABL)** is an uncommon subtype of acute leukemia characterized by clinical signs and symptoms related to **hyper-histaminemia**.
 - ▶ Patients usually present with bone marrow **(BM) failure** due to the infiltration of BM by the blasts and may or may **not** have **circulating** blasts.
- 



- ▶ ABL accounts for about 4–5% of all instances of acute nonlymphocytic leukemia, and it is associated with a wide age range of occurrence, rapid clinical progression, and poor outcomes.
 - ▶ Patients usually present with BM failure, cutaneous involvement due to high histamine levels, organomegaly, and lytic bone lesion.
- 

- ▶ Myeloid markers such as **CD13** and **CD33** are expressed by leukemic blasts, which are also positive for **CD123**, **CD203c**, and **CD11b**, but **KIT (CD117)** is **negative**.
- ▶ **t(X;6) (p11; q23)** translocation resulting in the **MYB–GATA1** fusion gene has been seen in sporadic cases of **ABL**.
- ▶ **ABL** should be **differentiated** from **AML** with **t(6;9)**, blast **crisis phase** of **CML**, **AML** with **BCR–ABL1** fusion gene, and **acute promyelocytic** leukemia with basophilic differentiation.

Primary myelofibrosis



- ▶ Primary myelofibrosis (PMF) is a rare bone marrow blood cancer. It is classified by the World Health Organization (WHO) as a type of myeloproliferative neoplasm.

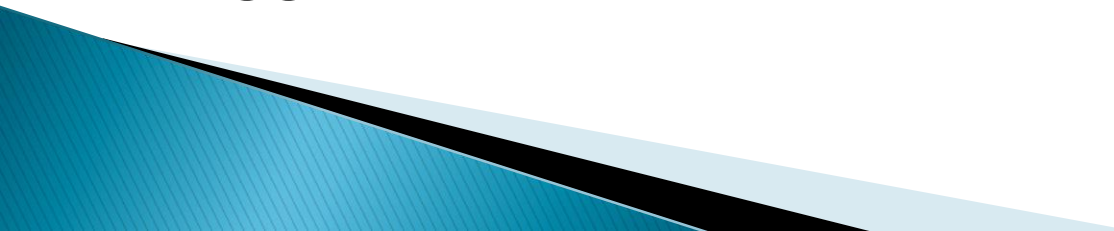
- ▶ This is most often associated with a somatic mutation in the JAK2, CALR, or MPL gene markers.
- ▶ In PMF, the healthy marrow is replaced by scar tissue (fibrosis), resulting in a lack of production of normal blood cells. Symptoms include anemia, increased infection and an enlarged spleen (splenomegaly)

MASTOCYTOSIS

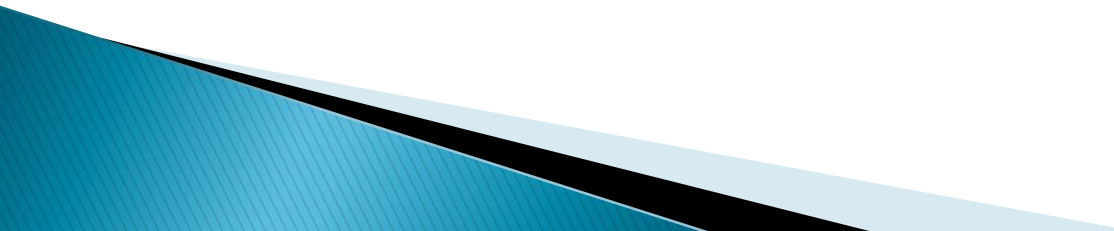


Mastocytosis

Mastocytosis

- ▶ **Mastocytosis** is a condition where **mast cells**, build up under the **skin** and/or in the **bones**, **intestines** and other organs.
 - ▶ This abnormal growth of mast cells causes a range of symptoms, including **itchy** bumps on the skin, gastrointestinal (GI) issues such as **diarrhea**, and **bone pain**.
 - ▶ It can increase the risk of **anaphylaxis** allergic when patients come across certain environmental triggers (such as a **bee** sting).
 - ▶ In some cases, the mastocytosis can be aggressive and lead to **death** if left untreated.
- 

- ▶ **There are two main types of mastocytosis:**
- ❖ **Cutaneous:** It occurs more often in **children**. people with the disorder have significant symptoms include much higher risk of a **severe allergic** reaction, which can be **fatal**.
- ❖ **Systemic:** Occurring mainly in **adults** .Mast cells accumulate in the **bone** marrow and organs, such as the **intestines**. In cases of aggressive systemic mastocytosis, it can be life-threatening as mast cell **leukemia** and mast cell **sarcoma**.

- ▶ **To diagnose cutaneous mastocytosis:**
 - ❖ a skin biopsy in cutaneous mastocytosis
 - ❖ a **bone marrow biopsy** in systemic mastocytosis.
 - ❖ the basal serum total **tryptase** level. Mast cells release tryptase, an enzyme, when the cells are triggered.
- 

- ▶ **How is mastocytosis treated?**
 - ▶ , you'll need to **avoid triggers** that might cause an attack.
 - ▶ **Medications for symptoms:** **Antihistamines**, leukotriene modifiers, mast cell stabilizers and **corticosteroid** creams can relieve the symptoms
 - ▶ **Epinephrine:** Everyone who has mastocytosis should carry an **EpiPen**
 - ▶ **Ultraviolet light:**
- 

- ▶ **Treatments for aggressive systemic mastocytosis:** chemotherapy such as **cladribine** to treat aggressive systemic mastocytosis.
- ▶ **Midostaurin**, a drug that **targets** the **KIT** mutation has been **approved** by the US **FDA** for the treatment of systemic mastocytosis.
- ▶ For those **without** a mutation in the **KIT** gene, another medication called **imatinib** can be used.
- ▶ **MBT**
- ▶ .A new medication that targets the KIT mutataion, called **avapritinib**, while **not** approved by the US FDA

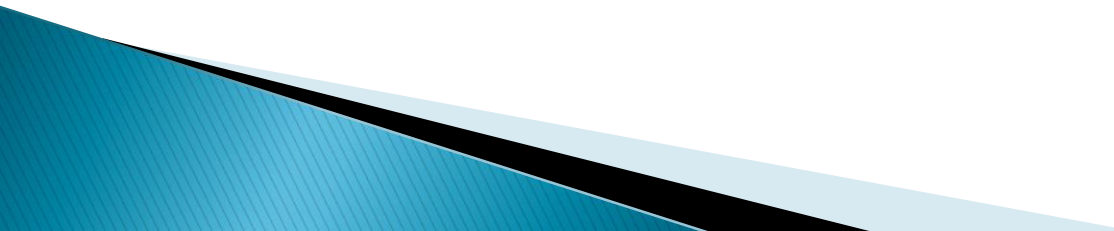
- ▶ The second category involves:
 - ❖ chronic inflammation
 - ❖ tuberculosis,
 - ❖ chicken pox
 - ❖ parasitic infections, Ticks
 - ❖ inflammatory bowel disease,
 - ❖ rheumatoid arthritis.
 - ❖ Multiple sclerosis
 - ❖ Hypothyroidism
 - ❖ Crohn's disease
 - ❖ Lupus nephritis
 - ❖ iron deficiency

- ▶ The third category is allergic including:
 - ❖ food and drug allergies
 - ❖ allergic rhinitis.
 - ❖ Autoimmune urticaria
- The degree of basophilia may correlate with symptoms.

Approach to suspected basophil disorders

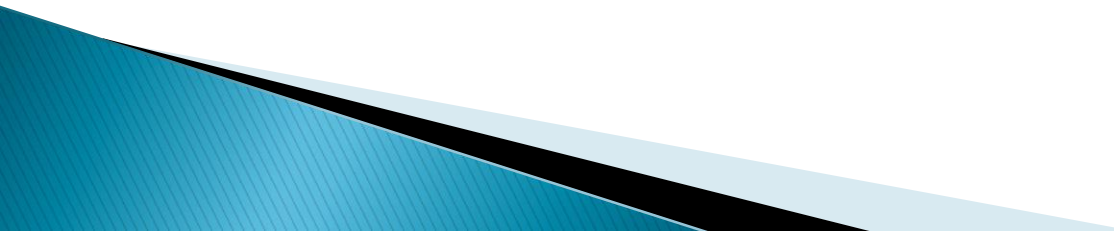
- ▶ **Transient** abnormalities of basophil number are **more likely** to be **reactive** process
- ▶ while **persistent basophil** counts above **1000** cells $> \mu\text{l}$ should lead to suspicion of a **neoplastic** process

The history should focus on :

- ▶ Medications
 - ▶ Diet
 - ▶ Atopy
 - ▶ Recent contacts
 - ▶ Travel
 - ▶ Infectious symptoms
 - ▶ Past medical history
 - ▶ Symptoms seen in leukemia
- 

Physical examination should include :

- ▶ Atopic conditions such as :
 - ❖ Urticaria, allergic rhinitis, bronchial wheezing, infectious signs
- ▶ Evidence of cytopenias such as :
 - ❖ Pallor, bruising, petechiae

- ▶ The **most** important physical **examination** finding in regards to basophilia is the spleen. If **splenomegaly** is present, the likelihood of finding a **myeloproliferative** syndrome is very high.
 - ▶ occasionally in CML and primary **myelofibrosis**, splenomegaly can be **massive**.
- 

- ▶ An essential first step is examination of the **peripheral blood** smear. Key findings on the smear include **a left-shift**, defined as an increase in early or premature forms of WBCs in the peripheral blood.

- ▶ Another crucial test is Janus kinase 2 (**JAK2**) genotyping, an acquired genetic mutation that is found in **95%** of patients with **polycythemia** vera, **50%** of patients with primary **myelofibrosis** and **50%** with essential **thrombocythemia**.
- ▶ More recently, calreticulin (**CALR**) has been found to be mutated in roughly **30%** of patients with primary **myelofibrosis** and essential **thrombocythemia**, while mutations in the **myeloproliferative** leukemia (MPL) are found in **5%** of cases

- ▶ the Philadelphia translocation, **BCR/ABL** testing for **CML**. This finding is diagnostic for CML

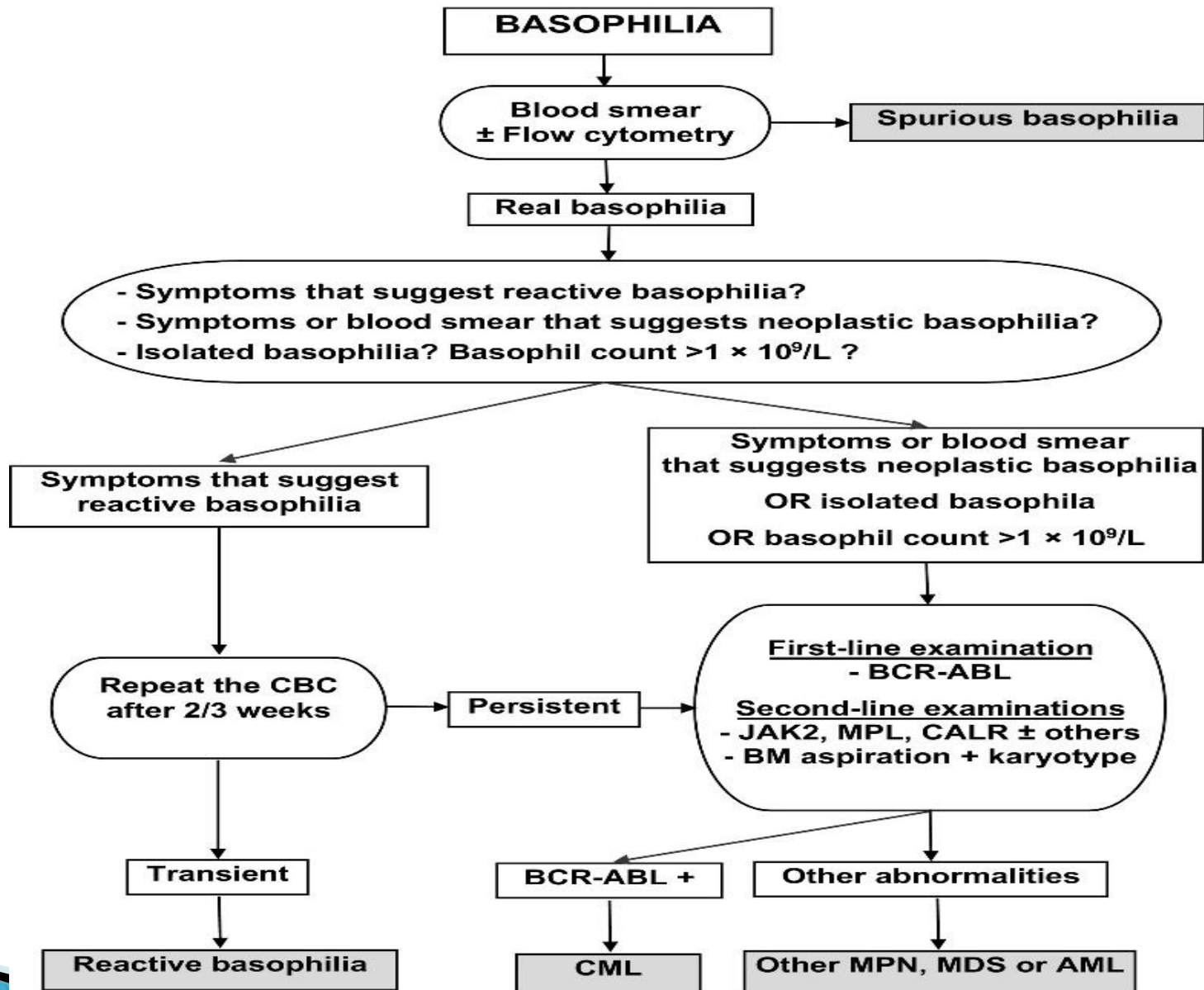
- ▶ In **mast cell** diseases, **tryptase** is an appropriate screening test.
- ▶ Tryptase can also be elevated in **hypereosinophilic** syndrome

- ▶ **BMA** is usually not necessary when diagnosing a **myeloproliferative** disease (**except myelofibrosis**), but it is essential in diagnosing **myelodysplastic** syndrome and acute **leukemia** .

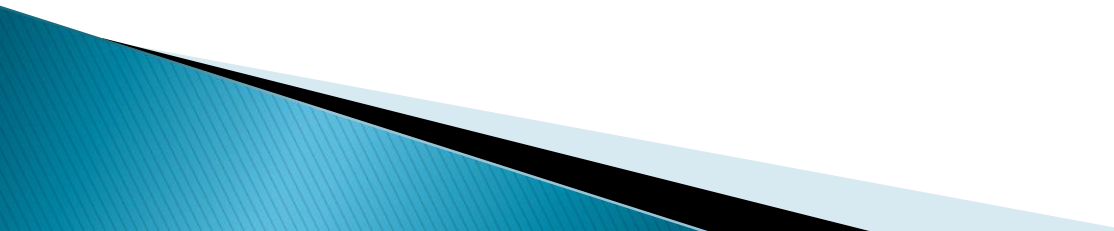
- ▶ **Peripheral blood flow cytometry** is useful **only** if the above findings suggest **acute leukemia**. It is typically **not helpful** in most **myeloproliferative** diseases or **myelodysplastic** syndrome.
- ▶ The **exception** is idiopathic **myelofibrosis** when **high levels** of cluster of differentiation molecule 34 (**CD34**) and WBCs can be detected in peripheral blood.

- ▶ in concerning patients :
- ▶ **BMA/B** with morphology, **flow cytometry** , cytogenetic, **molecular** evaluation for MDS, myeloproliferative disorders including:
 - ▶ **BCR-ABL** , **Jak2** , **CALAR** , **MPL** should be conducted

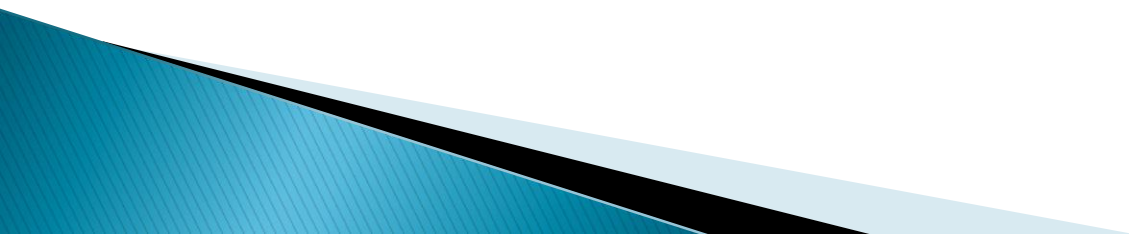
- ▶ Patients that are more likely to have a **reactive** basophilia may be **watched** with repeated **CBCs** with persistent, **rising**, or other findings concerning a bone **marrow** process prompting malignancy evaluation.



Treatment of basophilia

- ▶ **Most** cases of abnormal basophil number are **reactive** and benign and no targeted therapy against the basophil
 - ▶ Treating the **underlying** condition should result in improvement in count abnormality
 - ▶ Patients with **malignant** conditions should undergo **appropriate** therapy, including tyrosine kinase inhibition, chemotherapy and/or HSCT
- 

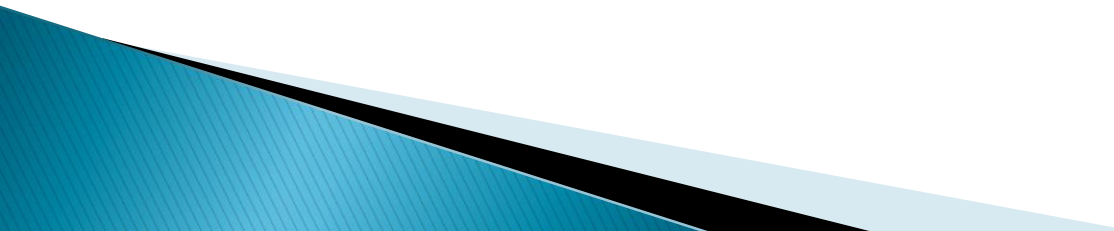
- ▶ Patients with **marked** basophophilia may have symptoms attributable to the release of biogenic **amines** or **heparin-like** material from degranulated basophils and may benefit from the administration of **antihistamines**

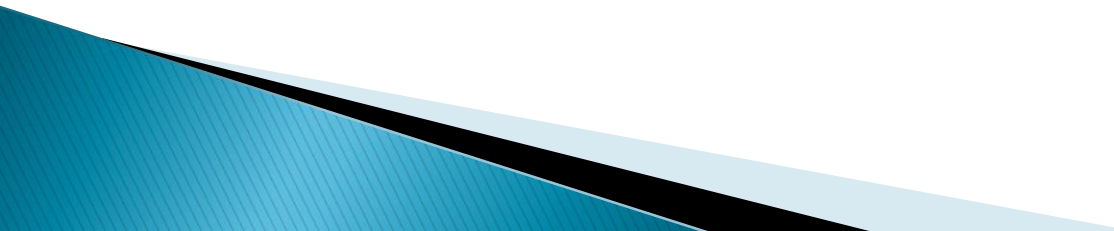


The Basopenia

- ▶ Basopenia (or basocytopenia) is a form of agranulocytosis associated with a deficiency of basophils
- ▶ It is difficult to detect without flow cytometry, because normal levels are so low. It can be defined as less than $0.01 \times 10^9 / L$.^[4]

Approach to basopenia

- ▶ Chronic urticarial
 - ▶ Glucocorticosteroid administration
 - ▶ Cushing disease
 - ▶ Chronic inflammation
 - ▶ Hypersensitivity reactions
 - ▶ Anaphylaxis
 - ▶ Drug-induced reactions
 - ▶ Leukocytosis (in association with diverse disorders)
- 

- ▶ Thyrotoxicosis and after treatment with thyroid hormones and may be increased in myxedema
 - ▶ **Congenital** basopenia is very **rare** and may be associated with the **absence** of **eosinophils**.
 - ▶ **Ovulation**
- 

- ▶ At the time of **ovulation** a **statistically significant decrease** in the number of basophil count was noted.
- ▶ Basopenia at the time of ovulation was probably due to **migration** of these cells from the peripheral blood towards the rupturing follicle for the release of **histamine required** for **ovulation**.

Thanks you for pay attention

