
# Lecture 8: Chronic Leukemia

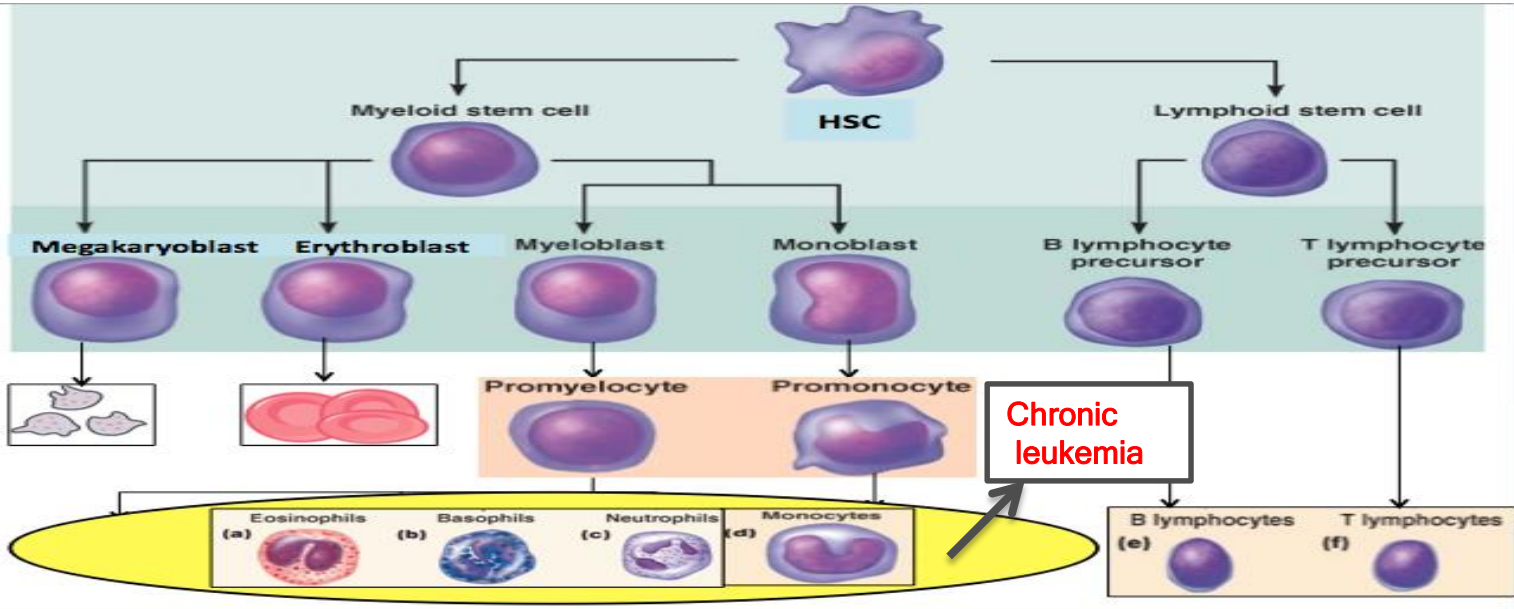
Myelodysplastic syndrome

# Chronic Leukemia

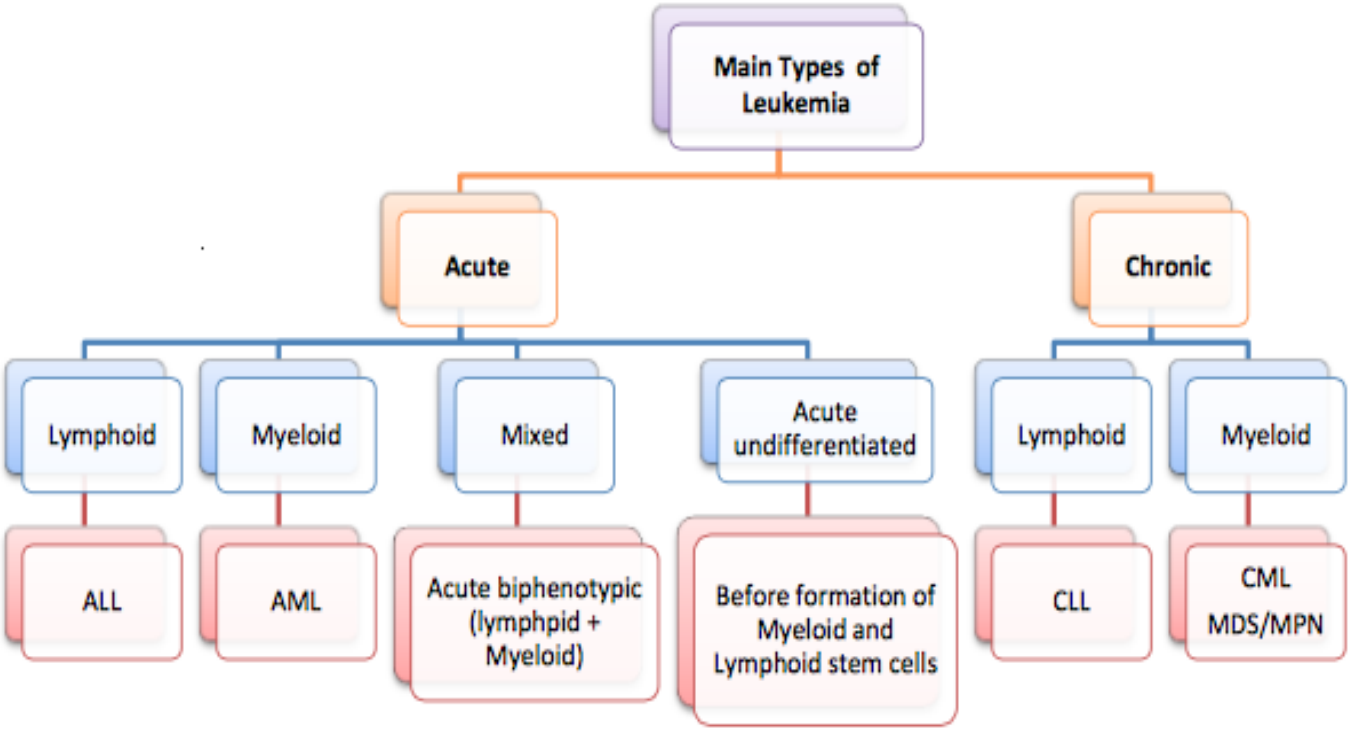
- Heterogeneous group of hematopoietic neoplasms .
- Uncontrolled proliferation and decreased apoptotic activity with variable degrees of differentiation (Chronic leukemia unregulated growth of mature cells unlike the acute leukemia which is immature "precursors") .
- Composed of relatively mature cells
- precursors are also present in circulation but mainly mature cells.
- Indolent

- (If untreated, the course is in months or years)
- (patient could be asymptomatic for years).

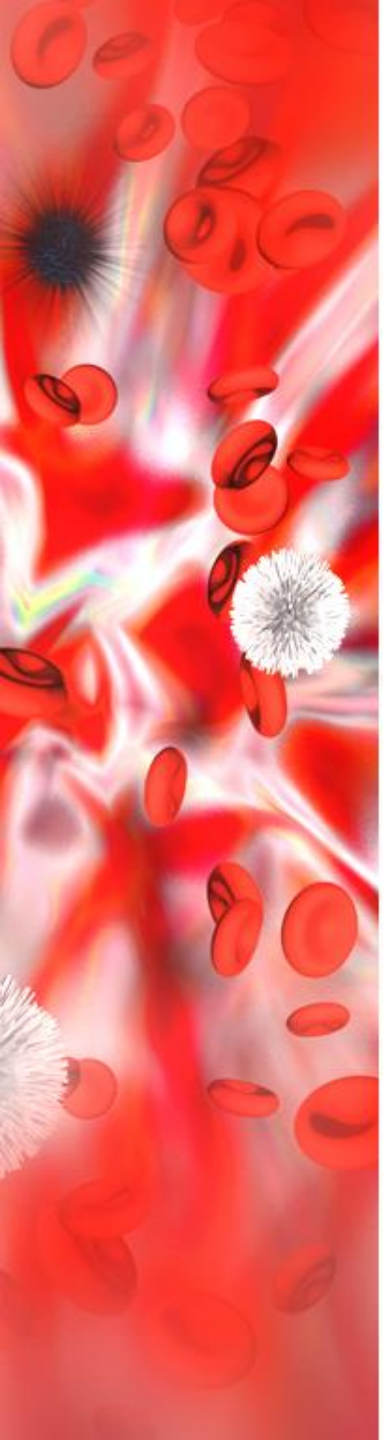
- Occurs mainly in adults.



# Main types of leukemia




- Leukemia can be divided on the basis of the speed of evolution of the disease into acute (rapid,weeks to months) and chronic (slow,asymptomatic for years).
- Each of these is subdivided into myeloid and lymphoid according to the cell type involved



# Myeloproliferation neoplasms

- Malignant proliferation of myeloid cells (maturing cells) which are mainly granulocytes in blood and bone marrow.
- Occur mainly in adults
- Slow onset and long course

# MPN features

- Cytosis (increase in number of cells)
- Organomegaly (mainly splenomgaly) should be enlarged spleen to be MPN
- High uric acid (patients might develop gout)
- Hypercellular bone marrow
- Progression to acute leukemia mainly AML but never to ALL.

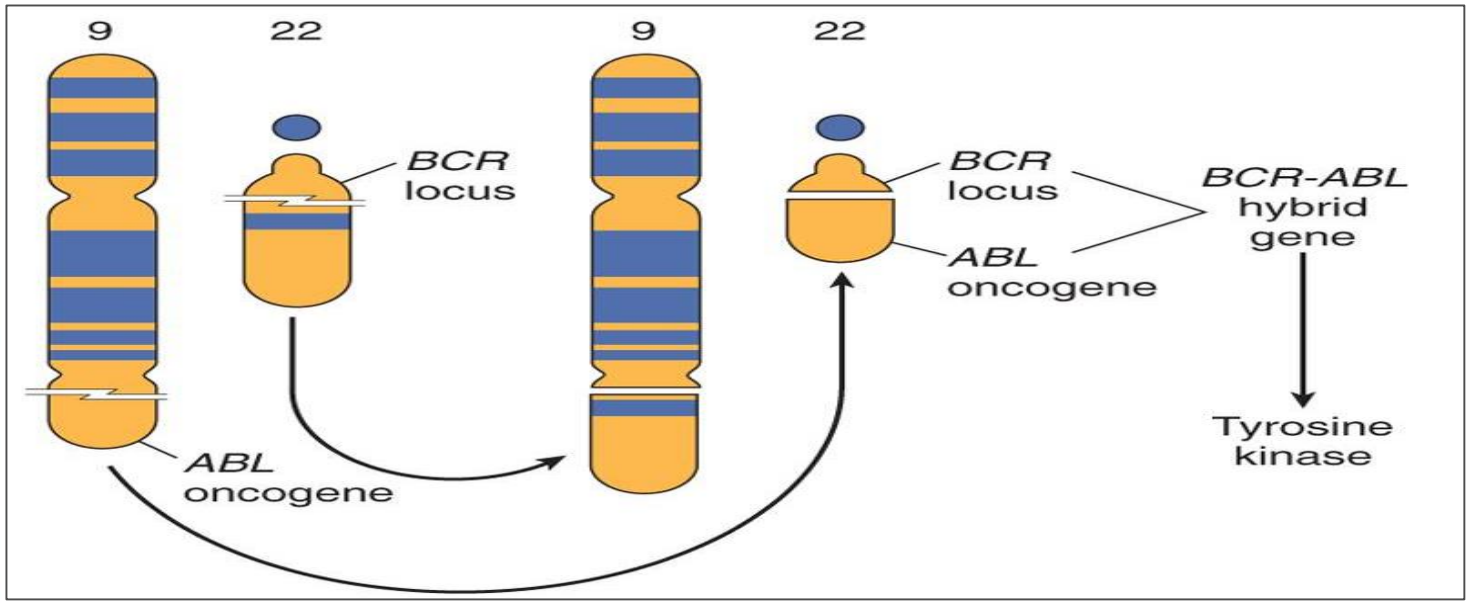
# Chronic Myeloid Leukemia (CML)

- Stem cell MPN.
- Predominant proliferation of granulocytic cells.
- Consistently associated with the BCR-ABL1 fusion gene located in the Philadelphia (Ph) chromosome which results from t(9;22) .

# Clinical Presentation of (CML)

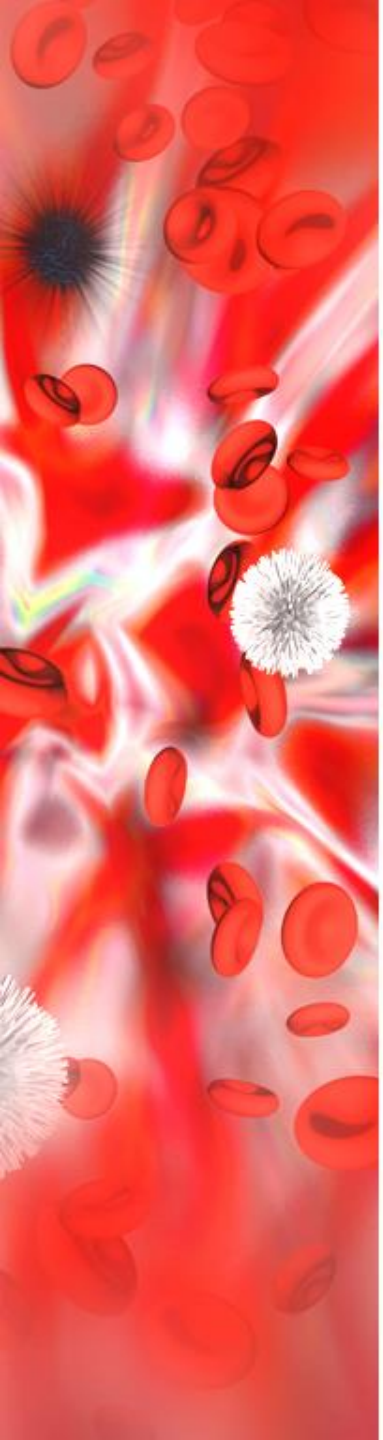
- Asymptomatic presentation (20-40%) silent
- Routine CBC : marked leukocytosis .
- Common symptoms : Fatigue ,weight loss or night sweating .
- Abdominal discomfort due to splenomegaly .
- Splenomegaly **(Massive)** .

# Pathogenesis of CML




Tyrosine Kinase : is an enzyme involved in the activation of all steps of the transduction pathway of cellular proliferation.

TK activity is increased abnormally when BCR gene and ABL1 gene are fused in Philadelphia chromosome (Uncontrolled proliferation).



# Main Differential Diagnosis

1) Chronic myelomonocytic leukemia (CMML): monocytosis, BCR-ABL –ve.

2) Leukemoid reaction: leukocytosis due to physiological response to stress or infection.

| | CML | Leukaemoid |
|---|---|---|
| **Age** | Adult | Any age |
| **WBC count** | High (200,000-300,000) | High but <100,000 |
| **Differential** | Mainly myelocytes and segmented neutrophils | Mainly Bands |
| **Morphology** | Hypogranular | Toxic (infection) |
| **Splenomegaly** | + (Huge) | -/+ (Mild) |
| **NAP score** | Low | High |
| **BCR/ABL** | **+ve** (disease) | **-ve** (normal) |
| **Onset** | Chronic | Acute |

**Neutrophil Alkaline Phosphatase (NAP) score :**
**Cytochemical stain that estimate the amount of alkaline phosphatase enzyme in neutrophilis .**

# Chronic Myeloid Leukemia Phases

**Chronic phase**

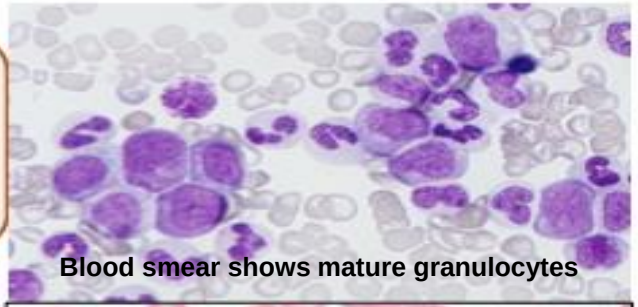
- Leukocytosis (12-1000×10⁹/L)
- Mainly neutrophils & myelocytes
- Blasts ≤10% ,Basophils≤ 20%
- Stable course (years)

**Accelerated phase**

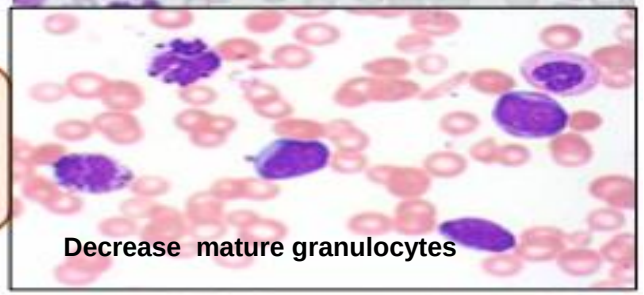
- Increasing counts
- 10-19% blasts (basophils ≥20%)
- Unstable course (months)

**Blastic phase**

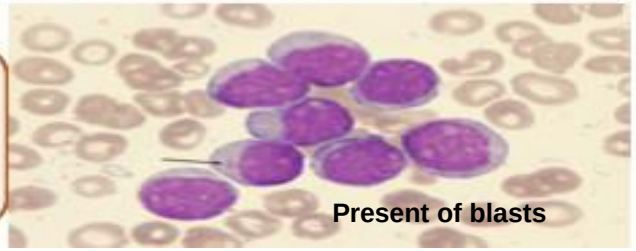
- ≥20% blasts = Acute Leukemia
- 80% AML & 20% ALL WHY ?
- (coarse: Weeks)



Blood smear shows mature granulocytes



Decrease mature granulocytes



Present of blasts

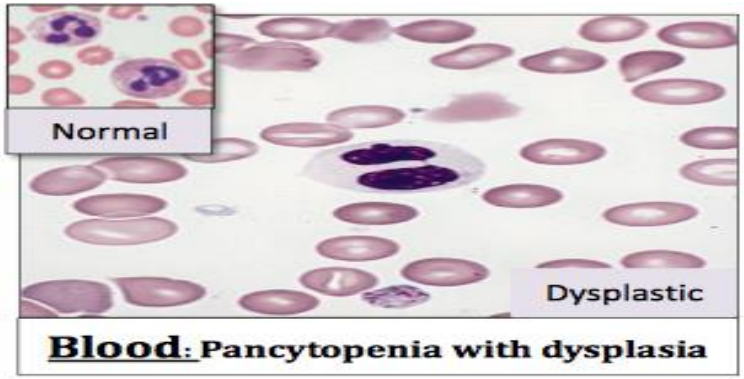
## CML Treatment

1st line therapy: tyrosine kinase inhibitors like Imatinib
- Excellent response (5 years survival > **90%**).
2nd line therapy : if no response => stem cell transplantation.

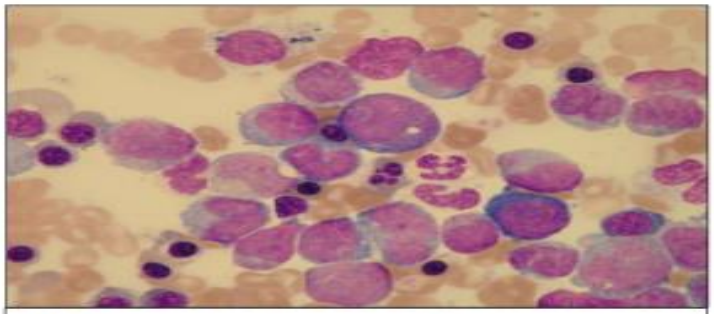
# Myelodysplastic Syndromes (MDS)

Group of myeloid neoplasm's characterized by:

1- Peripheral cytopenia (low HB ± low WBC & low PLT).
2- Dysplasia (abnormal morphology).
3- Ineffective hematopoiesis (hypercellular bone marrow).
4- Progression to AML (preleukaemic disease).
5- Enhanced apoptosis.




**Blood**: Pancytopenia with dysplasia



**BM**: Hypercellular with dysplasia

Proliferation — Apoptosis = Ineffective Hematopoiesis

- Many subtypes according to:

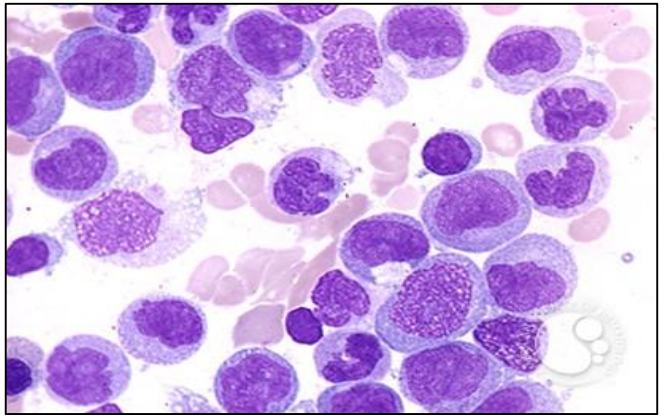
1-Blast count 2-Degree of dysplasia 3-Genetics

- Variable genetic abnormalities mainly -5, -7
- Treatment : supportive +/- chemotherapy

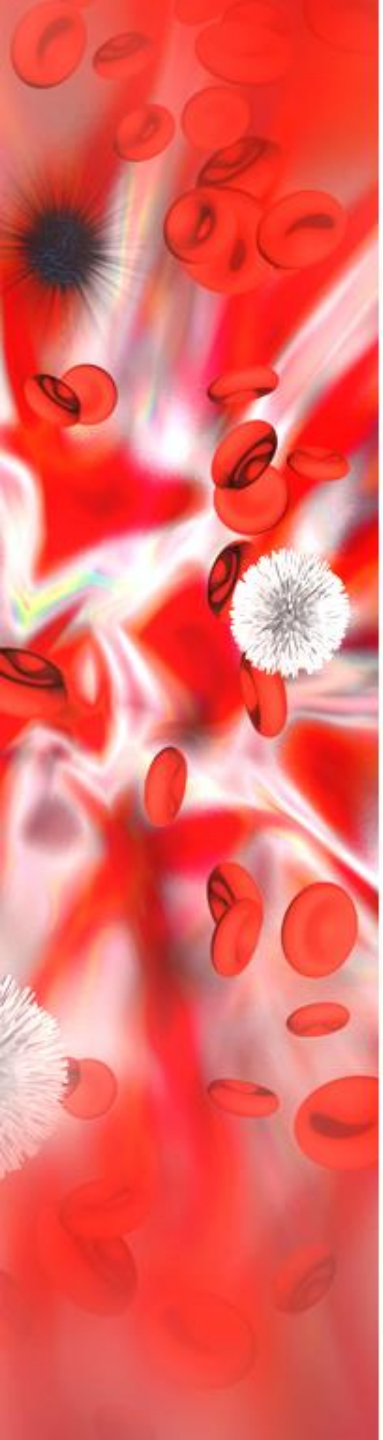
# Chronic Myelomonocytic Leukemia (CMML)

- Clonal hematopoietic malignancy characterized by proliferation of both monocytes & neutrophils.
- MDS/MPN disease (Combination of both).
  * Features of MDS (dysplasia & enhanced apoptosis).
  * Features of MPN (marked proliferation).
- Philadelphia chromosome must be negative.
- Blast must be less than 20% (chronic leukemia) if 20% and above=> it will be acute leukemia.

- Aggressive course (survival rate around 2.5 years )
- Treatment : Chemotherapy ± SCT*



*Stem cell transplantation



# Summary from Essential Hematology for Chronic myeloid leukemia (CML)

- Chronic myeloid leukaemia is a clonal disorder of a pluripotent stem cell. The disease accounts for around 15% of leukaemias and may occur at any age.
- All cases of CML have a translocation between chromosomes 9 and 22. This leads to the oncogene *ABL1* being moved to the *BCR* gene on chromosome 22 and generates the Philadelphia chromosome.
- The resulting chimeric *BCR-ABL1* gene codes for a fusion protein with tyrosine kinase activity.
- In most patients the Philadelphia chromosome is seen by karyotypic examination of tumour cells but the molecular rearrangement may sometimes only be detected by FISH or PCR.
- The disease can occur at any age but is most common between the ages of 40 and 60 years.
- The clinical features include anaemia, bleeding and splenomegaly. There is usually a marked neutrophilia with myelocytes and basophils seen in the blood film.
- Transformation to an accelerated phase or acute leukaemia may occur.
- Treatment is with tyrosine kinase inhibitors such as imatinib, dasatinib or nilotinib. Tumour cells can acquire resistance to treatment and drug therapy is tailored in response to this.
- Stem cell transplantation can be curative and may also be useful for advanced disease.
- The clinical outlook is now very good and patients can expect long-term control of disease.
- Chronic eosinophilic and neutrophil leukaemias are much rarer.

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