# Acute Leukemia

- Physical findings
  - Splenomegaly
  - Mucocutaneous or GI bleeding
  - easy bruising
  - infection symptoms ( fever )
  - extramedullary manifestations like invasion of the gums
  - anemia
  - thrombocytopenia and leukocytosis ( non functional ) they are all blasts
  - associated with DIC ( prolonged PT PTT TT )
- Leukemias : Clonal expansion of bone marrow cells by malignant hematogenous cells
- AML is a disease of getting old due to clonal hematopoiesis due to increased mutations ( the survival is reduced with age )
- mechanism : arrest in the maturation process of hematopoiesis resulting in production of abnormal blasts ( myeloid or lymphoid ) or reduced hematopoiesis ( bone marrow failure )
- Acute Myeloid Leukemia risk factors
  - age
  - genetic disorders : down / patau / neurofibromatosis
  - environmental : benzene / pesticides / smoking
  - radiation therapy
  - chemotherapy : Alkylating agents and topoisomerase 2 inhibitors
- it can be primary ( de novo ) or secondary to MDS MPD
- New approach in treating AML
- Classification of AML based on morphology
  - M0 : undifferentiated
  - M1 : myeloblast without differentiation
  - M2 : myeloblast with differentiation
  - M3 : promyelocytic
  - M4 : myelomonocytic
  - M5 : monocytic
  - M6 : erythroid
  - M7 : Megakaryoblastic
- AML symptoms
  - Bone Marrow Failure
    - Anemia : fatigue pallor dyspnea
    - Thrombocytopenia : bleeding bruising
    - Neutropenia : fever with or without infections

    - Leukemic infiltration if tissues
        - hepatomegaly or splenomegaly or the tonsils
        - gingival or CNS infiltration
        - bone pain
        - lymphadenopathy
        - leukemia cutis ( skin manifestations )
    - Tumor Lysis Syndrome
        - hyperuricemia
        - hyperphosphatemia
        - hyperkalemia
        - hypocalcemia
        - acute renal failure
        - metabolic acidosis
        - cardiac arrhythmias
    - Hyperleukocytosis ( leukostasis syndrome )
        - dyspnea and chest pain
        - headache and altered mental status
        - cranial nerve palsies
    - hyperviscosity
    - release of granules : gout
- Diagnosis
    - Blast count in the blood or bone marrow
        - 5%-20% : MDS
        - > 20% : leukemia
    - Flow cytometery
- Treatment
    - Remission induction ( stopping the clonal expansion )
        - 7+3 : cytarabine for 7 days then anthracycline for 3
    - post remission treatment ( consolidation )
        - chemotherapy
        - allo-BMT
    - new treatment methods
        - Risk stratification
        - Incorporation of Monoclonal antibodies
        - Incorporation of small melcules and targeted therapy
- Promyelocytic leukemia M3
    - Associated with t(15;17) mutation involving the retinoic acid receptor RAR gene

    - Good prognosis category
    - Commonly associated with DIC
    - blood film shows Promyelocytic with Prominent Auer rods
    - treatment of M3 : Tretinoin ( all trans retinoic acid ) only effective in M3 leukemia
    - using cytarabine might lead to DIC
    - ATRA Syndrome
        - Tretinoin does not produce DIC but produces another complication called the retinoic acid syndrome Occurring within the first 3 weeks of treatment
        - it is characterized by fever, dyspnea, chest pain, pulmonary infiltrates, pleural and pericardial effusions, and hypoxia
        - Glucocorticoids, chemotherapy, and supportive measures can be effective
        - The mortality of this syndrome is about 10%
- Auer rods is only seen in myeloid leukemia not lymphoid
- Myelomonocytic leukemia M4
    - associated with inverted 16 and eosinophilia
    - this is a good prognostic category
    - Associated with leukemia cutis
    - CNS disease may occur

**Acute Lymphoid Leukemia**

- Risk classification in ALL
    - Standard risk
    - High risk
    - Very high risk
- High-risk ALL/ very high risk
    - Pre - T
    - Pro - B
    - Age > 35 years,
    - WBC > 30 G/L in B ALL and > 100 G/L in T ALL
    - No remission after 4 weeks of induction therapy
    - Chromosome Philadelphia - positive or BCR/ABL (+)
- the choice of treatment-strategy depends on:
    - Risk Stratification
    - Immunophenotype of leukemic cells
        - T lineage,
        - early B lineage,

        - mature B lineage
    - Age and biological condition
    - Goal of treatment
- Treatment
    - CNS prophylaxis : Intrathecal methotrexate / Ara C / Steroids / Craniospinal irradiation
    - Induction : to restore the levels back to normal
    - Consolidation : chemotherapy or Allo BMT ( to prevent the emergence of resistant clones )
    - maintenance : methotrexate and steroids
- Allo BMT for ALL at high risk not responding to induction therapy

# Chronic Leukemia

- the symptoms are more subtle and less severe than acute
- the degree of pancytopenia is less than acute

### Chronic Lymphocytic Leukemia

- monoclonal proliferation of dysfunctional malignant B cells
- present in all ages but more aggressive in younger ages
- Symptoms
    - main clinical feature is diffuse painless bilateral lymph node enlargement ( lymphocytosis described as Morphologically mature and Immunologically immature )
    - splenomegaly
    - bacterial infections
    - Hypogammaglobulinaemia
- Flowcytometry shows CD19+ and CD20+ B cells ( diagnosis of choice no need for biopsy )
- smudge cells are present on blood film
- Staging
    - class 0 : lymphocytosis
    - class 1 : lymphocytosis with lymph node involvement
    - class 2 : lymphocytosis with organomegaly
    - class 3 : anemia
    - class 4 : lymphocytosis with thrombocytopenia
- the most common mutation is 13q del ( best prognosis ) and the worst one is p53
- treatment
    - the negatives of giving cytotoxic agents is worse than leaving the disease by itself to slowly progress
    - treatment does not depend on cytogenetics
    - treatment for symptomatic patients
    - main therapy is chemoimmumotherapy

### Chronic Myeloid Leukemia

- Characterized with abnormal proliferation of the granulocytic lineage of cell in the bone marrow ( neutrophils / basophils / eosinophils )
- divided into 3 stages

    - chronic phase : diagnosis phase : fatigue / weight loss / exercise intolerance / splenomegaly / leukocytosis ( no lymphadenopathy ) / blood film shows cells in all stages of development / high platelet count thus thrombosis  / gout / bone pain / Normochromic normocytic anemia
    - Accelerated phase : progressive anemia and splenomegaly / blasts present 10-20%
    - Blast phase ( crisis ) : blasts present > 20% / pegler huet anomaly ( hyposegmented neutrophils )
- Most common mutation ( characteristic ) is translocation between long arms of chromosomes 22 and 9 resulting in shortened chromosome 22 ( philadelphia chromosome ABL BCR mutation )
- no need to do bone marrow biopsy since the diagnosis of choice is chromosomal study ( karyptyping )
- Affects middle aged individuals and accounts for 20% of all leukemias affecting adults
- Treatment
    - Aim of treatment is to reduce WBC, prevent gout and target the molecular cause of the disease
    - The treament has been revolutionized by imatinib mesylate
    - Stem cell transplant SCT  is the only definitive therapy and treatment of choice in some patients
- Imatinib mesylate
    - Competitive inhibition at the ATP binding site of the Abl kinase
    - Rapid hematologic response
    - 95% of patients achieved complete hematologic remission, and 60% achieved major cytogenetic remission within few months
    - Side effects
        - The main side effects are fluid retention, nausea, muscle cramps, diarrhea and skin rashes
        - Myelosuppression is the most common hematologic side effect
    - Resistance develops due to Mutations at the kinase site
- Other Treatment Modalities
    - Alfa Interferons
    - Chemotherapy ( hydroxyurea, busulphan )
    - Allogeneic BMT