Acute basophilic Leukemia
WHO Acute basophilic Leukemia

- AML with primary differentiation to basophils.
- Some may represent blast transformation of an undetected Philadelphia chromosome BCR/ABL positive CML.
- Rare disease, < 1% of AMLs.
Clinically

- Features related to bone marrow failure.
- May be circulating blasts.
- Cutaneous involvement.
- Organomegaly.
- Lytic lesions.
- Hyperhistaminemia.
Morphology and Cytochemistry

• Blasts in blood and bone marrow.
  – Medium size, high N/C ratio.
  – Oval, rounded or bilobed nucleus with dispersed chromatin and 1-3 nucleoli.
  – Moderately basophilic cytoplasm and contains a variable number of coarse basophilic granules which may stain positive in metachromatic stains. There may be vacuoles.
Acute basophilic leukemia: bone marrow smear. Blasts and immature basophils. Granules vary from large coarse to smaller granules.
Morphology and Cytochemistry

• Blasts in blood and bone marrow.
  – Scanty mature basophils usually.
  – There may be dysplastic features in the erythroid precursors.
Blasts in blood and bone marrow.

- E.M.: granules contain structures characteristic of basophil precursors or mast cells:
  (1) an electron-dense particulate substance, internally bisected, or
  (2) a crystalline material arranged in a pattern of scrolls or lamellae (more typical of mast cells).

- Both granule types may be present in the same cell.
E.M. micrograph of an immature basophil. Speckled amorphous substance in granules. A granule contains a myelin figure.
Morphology and Cytochemistry

• Characteristic: metachromatic positivity with toluidine blue.

• Besides:
  - diffuse staining with acid phosphatase.
  - PAS positivity in blocks (some cases).
  - Blasts usually negative for SBB, MPO and NSE. Peroxidase activity can be ultrastructurally demonstrated.
Acute basophilic leukemia: toluidine blue reaction. Maturing basophils containing metachromatic granules.
Morphology and Cytochemistry

- Trephine biopsy:
  - Diffuse replacement by blast cells, sometimes with an increased number of basophil precursors.
  - Cases with mast cell differentiation: differentiated mast cells are close to the trabeculi. These cases often have prominent reticulin fibrosis.
Differential diagnosis

- Blast crisis of CML.
- AML subtypes with basophilia.
  - AML-M2 with 12p abnormalities or t(6;9).
  - Acute eosinophilic leukaemia.
  - Rare subtype of lymphoblastic leukemia with prominent coarse granules.
Differential diagnosis

• Clinical features, cytogenetics and blast cell morphology will distinguish between *de novo* cases from transformations of a CML and of an AML with basophilia.

• Immunological markers will distinguish between granulated ALL and acute basophilic leukemia.

• Cytochemistry for MPO and E.M. will distinguish basophilic from eosinophilic leukemia.
Immunophenotype

- Myeloid markers: CD13, CD33.
- Early haematopoietic markers: CD34, class-II HLA-DR.
- Usually blasts are CD9+ and some may be TdT+, but negative for specific lymphoid markers.
Genetics

- No consistent chromosome abnormality identified.
- 12p abnormalities or t(6;9), which may occur in AML with basophilia, are not identified.
- A few cases may present as de novo Philadelphia chromosome positive acute leukemia, with a t(9;22)(q34;q11).
Postulated cell of origin

- Early myeloid cell committed to the basophil lineage.

Prognosis

- Insufficient data available. Generally poor.
Acute panmyelosis with myelofibrosis
Acute panmyelosis with myelofibrosis

- Acute panmyeloid proliferation with accompanying fibrosis of the bone marrow.

- **Synonyms:**
  - Acute myelofibrosis
  - Acute myelosclerosis
  - Acute myelodysplasia with myelofibrosis
Epidemiology

- Very rare form of AML.
- Mainly adults, but also described in children.
- A de novo process or after treatment with alkylating agents and/or radiation.
Clinically

- Constitutional symptoms, weakness, fatigue.
- Marked cytopenia.
- No or minimal splenomegaly.
- Rapidly progressive evolution.
Morphology and Cytochemistry

• Marked cytopenia.

• RBCs:
  – No or minimal poikilocytosis.
  – Some anisocytosis.
  – Variable number of macrocytes.
  – Rare normoblasts.

Occasional immature neutrophils including blasts.
Morphology and Cytochemistry

• Dysplastic changes in myeloid cells.
• Atypical platelets may be noted.
• Unsuccessful bone marrow aspiration.
• Biopsy:
  – Hypercellular.
  – Variable hyperplasia of erythroid precursors, granulocytes and megakaryocytes.
  – Scattered foci of immature cells including blasts.
Acute myelofibrosis: trephine biopsy imprint. Several megakaryocytes with hypolobulated nuclei and blast forms.
Morphology and Cytochemistry

• Clusters of late erythroid precursors may be prominent.

• Conspicuous megakaryocytes, small to large with dysplastic features virtually always present.
  - Non-lobated nuclei with dispersed chromatin.
  - Uniformly eosinophilic cytoplasm, stained with PAS, FVIII, CD61.
Morphology and Cytochemistry

- Variable degree of fibrosis.

- Most have a marked increase in reticulin fibers.

- Uncommon collagenous fibrosis.
Acute myelofibrosis: trephine biopsy. Marked reticulin fibrosis and numerous megakaryocytes.
Acute myelofibrosis: trephine biopsy. Megakaryocytes with hypolobulated nuclei.
Differential diagnosis

- Acute megakaryoblastic leukemia.
- Acute leukemia with associated fibrosis.
- Metastatic tumor with a desmoplastic reaction.
- Chronic idiopathic myelofibrosis (CIMF).
- Distinction between acute panmyelosisis with myelofibrosis, AML-M7 with fibrosis, AML with multilineage dysplasia and fibrosis may be arbitrary and irrelevant clinically.
- Proliferative process involving all cell lines (granulocytes, erythroids and megakaryocytes) favors Acute Panmyelosis with Myelofibrosis.
Differential diagnosis

- Can be distinguished from CIMF by the predominance of more immature cells in the acute process and the characteristics of the megakaryocytes:
  - Acute process: dispersed chromatin and non-lobated or hypolobated nuclei. No or minimal splenomegaly (physical finding).
  - CIMF: condensed nuclear chromatin and contorted nuclei. Splenomegaly as a rule (physical finding).

- Metastatic tumor easier to identify with Immunostain studies.
Immunophenotype

- Phenotypic heterogeneity.
- Variable degree of expression of myeloid antigens.
- Blasts may express one or more myeloid antigens: CD13, CD33, CD117 and MPO.
- In some cases immature cells express erythroid or megakaryocytic antigens.
- Immunostains for multilineage antigens is recommended: MPO, lysozyme, CD41, CD61, FVIII, Gly-A, HbA.
Acute myelofibrosis: trephine biopsy. Megakaryocytes positive for FVIII-associated antigen (immunoperoxidase stain).
Genetics

• Complex abnormalities frequently involving chromosome 5 and/or 7.
Postulated cell of origin

- Myeloid hematopoietic stem cell.
- Fibroblastic proliferation is an epiphenomenon.

Prognosis

- Usually associated with poor response to chemotherapy and short survival.
Myeloid sarcoma
Myeloid sarcoma

• Definition
  – Tumor mass of myeloblasts or immature myeloid cells occurring in an extramedullary site or in bone
  – May precede or occur concurrently with acute or chronic myeloid leukemias, MPDs or MDSs
  – Initial manifestation of relapse in previously treated AML
Myeloid sarcoma

• **Synonyms**
  - Extramedullary myeloid tumor
  - Granulocytic sarcoma
  - Chloroma
Myeloid sarcoma

- Sites of involvement
  - Subperiosteal bone or skull, paranasal sinuses, sternum, ribs, vertebrae and pelvis
  - Lymph nodes
  - Skin
Myeloid sarcoma

• Clinical features
  – *de novo*
  – Concurrently or preceding AML
    • May precede AML by months to years
Myeloid sarcoma

• **Differential diagnosis**
  
  – Non-Hodgkin lymphoma
    • Lymphoblastic type
    • Burkitt lymphoma
    • Large-cell lymphoma
  
  – Small round cell tumors
    • Neuroblastoma, rhabdomyosarcoma, Ewing’s/PNET and medulloblastoma
Myeloid sarcoma

- **Immunophenotype**
  - **Myeloid blasts**
    - CD13, CD33, CD117, MPO
    - CD43
  - **Monoblasts**
    - CD14, CD116, CD11c, lysozyme, CD68
Myeloid sarcoma

• **Genetics**
  - Association with AML with maturation and $t(8;21)(q22;q22)$ and AMML Eo with $\text{inv}(16)(p13q22)$ or $t(16;16)(p13q22)$
  - 11q23 in monoblastic sarcoma

• **Cell of origin**
  - Primitive myeloid hematopoietic cell
Myeloid sarcoma

- **Prognosis**
  - Myeloid sarcoma in a setting of MDS or MPD is blast transformation
  - Myeloid sarcoma does not generally change the prognosis of the underlying leukemia
  - Isolated myeloid sarcoma
    - Radiotherapy may result in very prolonged survival
Acute Leukemias of Ambiguous Lineage
Acute Leukemias of Ambiguous Lineage

- **Definition**
  - Forms of acute leukemia in which the morphologic, cytochemical and immuno-phenotypic features of the blasts:
    - lack sufficient evidence to classify as myeloid or lymphoid origin
    - or, have morphologic and/or immunophenotypic characteristics of both myeloid and lymphoid cells (acute bilineal leukemia and acute biphenotypic leukemia).
    - or, have both B and T lineages (acute bilineal leukemia and acute biphenotypic leukemia).
Acute Leukemias of Ambiguous Lineage

• Synonyms
  – Acute leukemia of indeterminate lineage
  – Mixed phenotype acute leukemia
  – Mixed lineage acute leukemia
  – Hybrid acute leukemia
Acute Leukemias of Ambiguous Lineage

• **Epidemiology**
  - <4% of all acute leukemias
  - More frequent in adults

• **Etiology**
  - Unknown
  - Environmental toxins and radiation exposure
Acute Leukemias of Ambiguous Lineage

- Clinical features
  - Related to bone marrow failure
    - Fatigue
    - Infections
    - Bleeding
Acute Leukemias of Ambiguous Lineage

• Morphology
  – Acute undifferentiated leukemia
    • Leukemic cells lack any differentiating features
  – Acute biphenotypic and acute bilineal leukemias
    • May present as one subtype of AML
      – Monoblastic
      – Poorly differentiated myeloid
  • Features of ALL
Acute Leukemias of Ambiguous Lineage

• **Immunophenotype**
  – Undifferentiated acute leukemia
    • Leukemias lack specific lineage markers
      – CD79a, CD22, CD3 and MPO
    • Generally don’t express more than one lineage-associated marker
    • Often express HLA-DR, CD34, CD38, +/- TdT and CD7
Acute Leukemias of Ambiguous Lineage

• Immunophenotype (cont)
  – Bilineal acute leukemia
    • Dual population of blasts, each with distinct lineage
      – Myeloid and lymphoid, or
      – B and T lineages
    • May evolve into biphenotypic acute leukemia
Acute Leukemias of Ambiguous Lineage

• Immunophenotype (cont.)
  – Biphenotypic acute leukemia
    • Blasts co-express myeloid and T or B lineage markers
    • Or, concurrent B and T lineage markers
    • Rarely co-express markers for all lineages (myeloid, T, and B)
Biphenotypic acute leukemia
Acute Leukemias of Ambiguous Lineage

- Immunophenotype (cont.)
  - Co-expression of lineage-associated (not specific) markers is not sufficient for biphenotypic leukemia.
    - Myeloid-antigen positive ALL
    - Lymphoid antigen-positive AML
  - “Lineage switch” after therapeutic intervention
    - Possible expansion of pre-existing minor population of blasts of different lineage following therapeutic suppression of the major population
    - Possible lineage instability
Acute Leukemias of Ambiguous Lineage

- **Myeloid lineage:**
  MPO (flow, immuno, or cytochemistry)
  or
  Monocytic differentiation (2 of the following: NSE, CD11c, CD14, CD64, lysozyme)

- **T lineage:**
  CD3 (surface or cytoplasmic)

- **B lineage:**
  Strong CD19 with at least 1 of the following: CD79a, cCD22, CD10
  or
  Weak CD19 with at least 2 of the following: CD79a, cCD22, CD10
Acute Leukemias of Ambiguous Lineage

• Differential diagnosis
  – Biphenotypic acute leukemia
    • Myeloid antigen positive ALL
    • Lymphoid antigen positive AML
  – Undifferentiated acute leukemia
    • Minimally differentiated AML
    • Unusual precursor-B-cell or T-cell ALL
Acute Leukemias of Ambiguous Lineage

- Genetics
  - High degree of cytogenetic abnormalities
  - 1/3 have Ph chromosome
    - CD10(+) precursor B lymphoid component
  - t(4;11)(q21;q23)
  - 11q23
    - CD10 (−) precursor B population with a separate component of acute monocytic leukemia
Acute Leukemias of Ambiguous Lineage

• Genetics (cont.)
  – T/myeloid biphenotypic or bilineal leukemia do not show these cytogenetic findings (previous slide) but have other complex karyotypes

• Molecular diagnosis
  – Shows Ig and TCR rearrangements or deletions in many cases including those that present as “AML”
Acute Leukemias of Ambiguous Lineage

• Cell of origin
  – Multipotent progenitor stem cell

• Prognosis
  – Unfavorable, particularly in adults
  – t(4;11) or Ph particularly unfavorable

• Therapy
  – Usually aggressive chemotherapy
  – BMT