Acute basophilic Leukemia

WHO Acute basophilic Leukemia

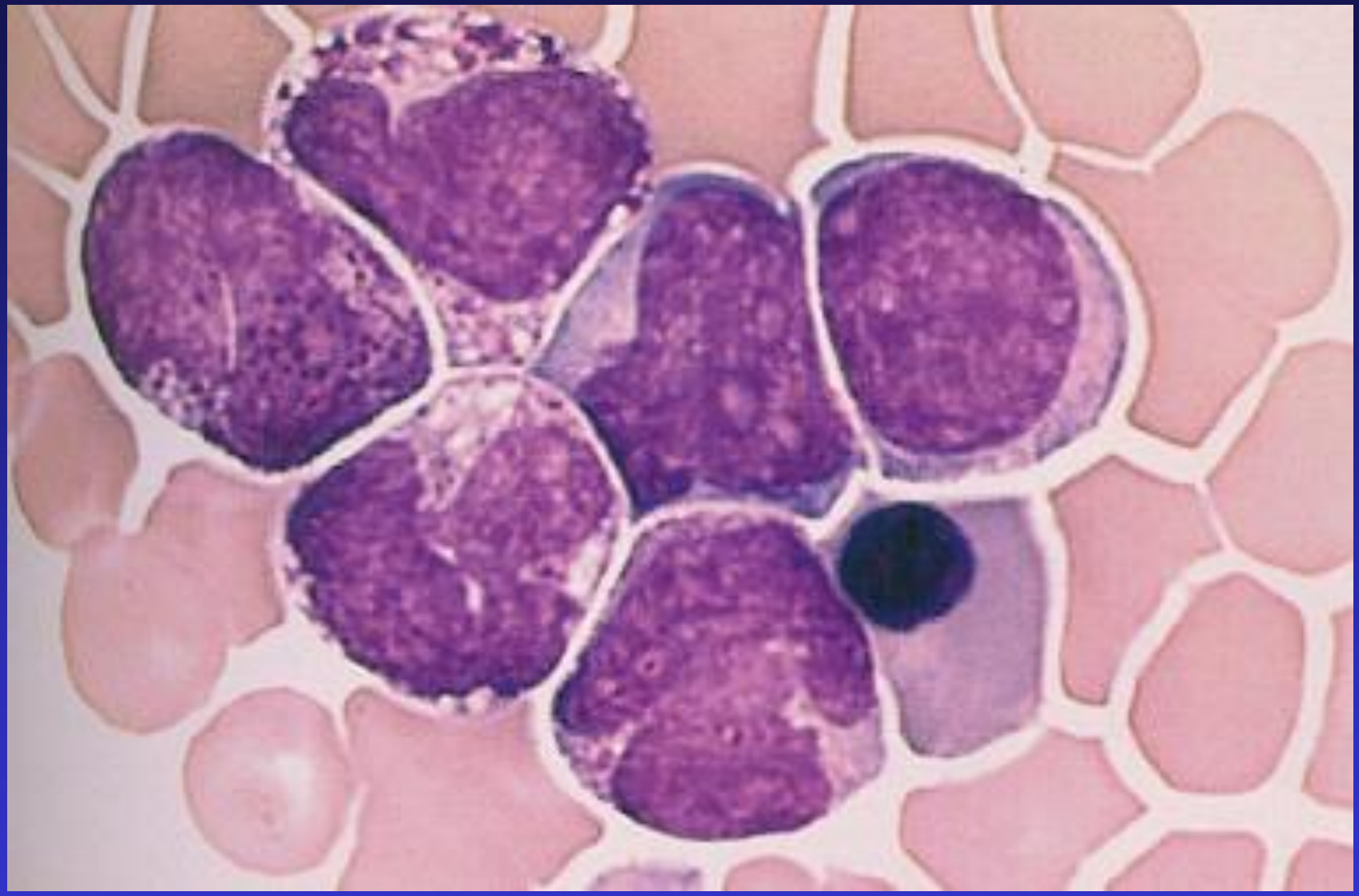
- AML with primary differentiation to basophils.
- Some may represent blast transformation of an undetected Philadelphia chromosome BCR/ABL positive CML
- Rare disease, < 1% of AMLs

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.
  - Moderatly 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.

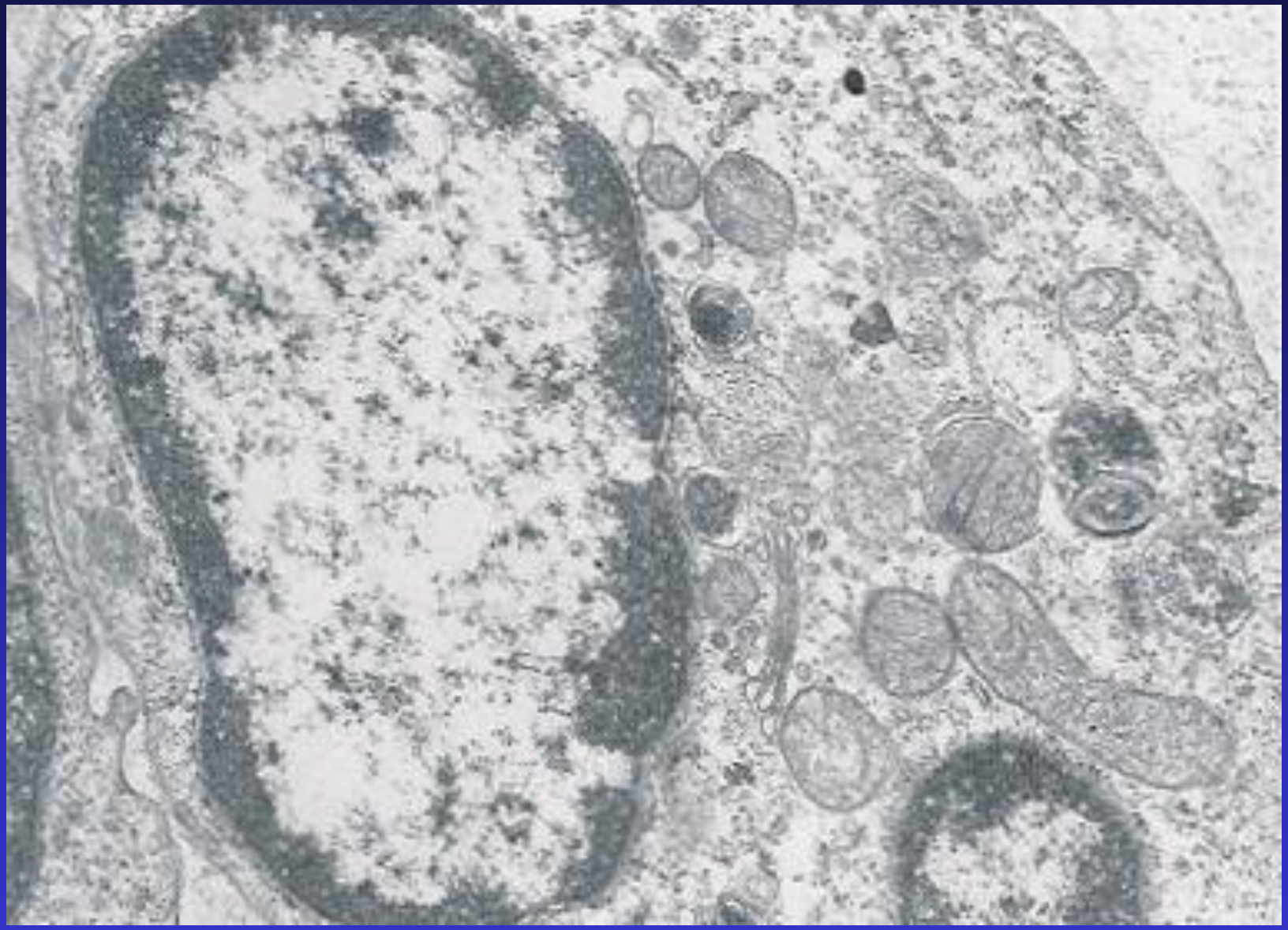
Morphology and Cytochemistry

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

Morphology and Cytochemistry

- 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

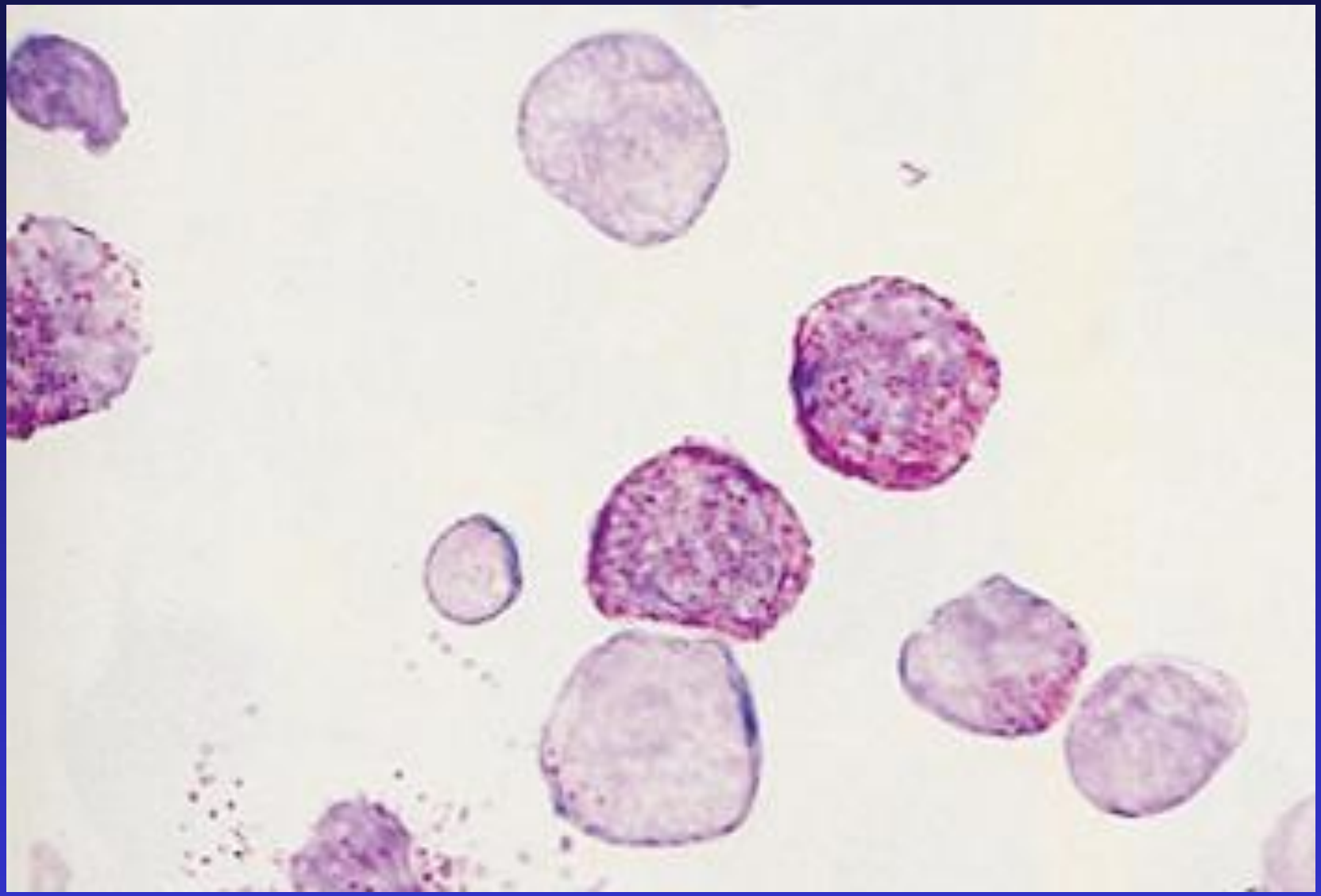
    (2) a crystalline material arranged in a pattern of scrolls or lamellae (more typical of mast cells).
  - Both granule types may be present in the same cell.



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.

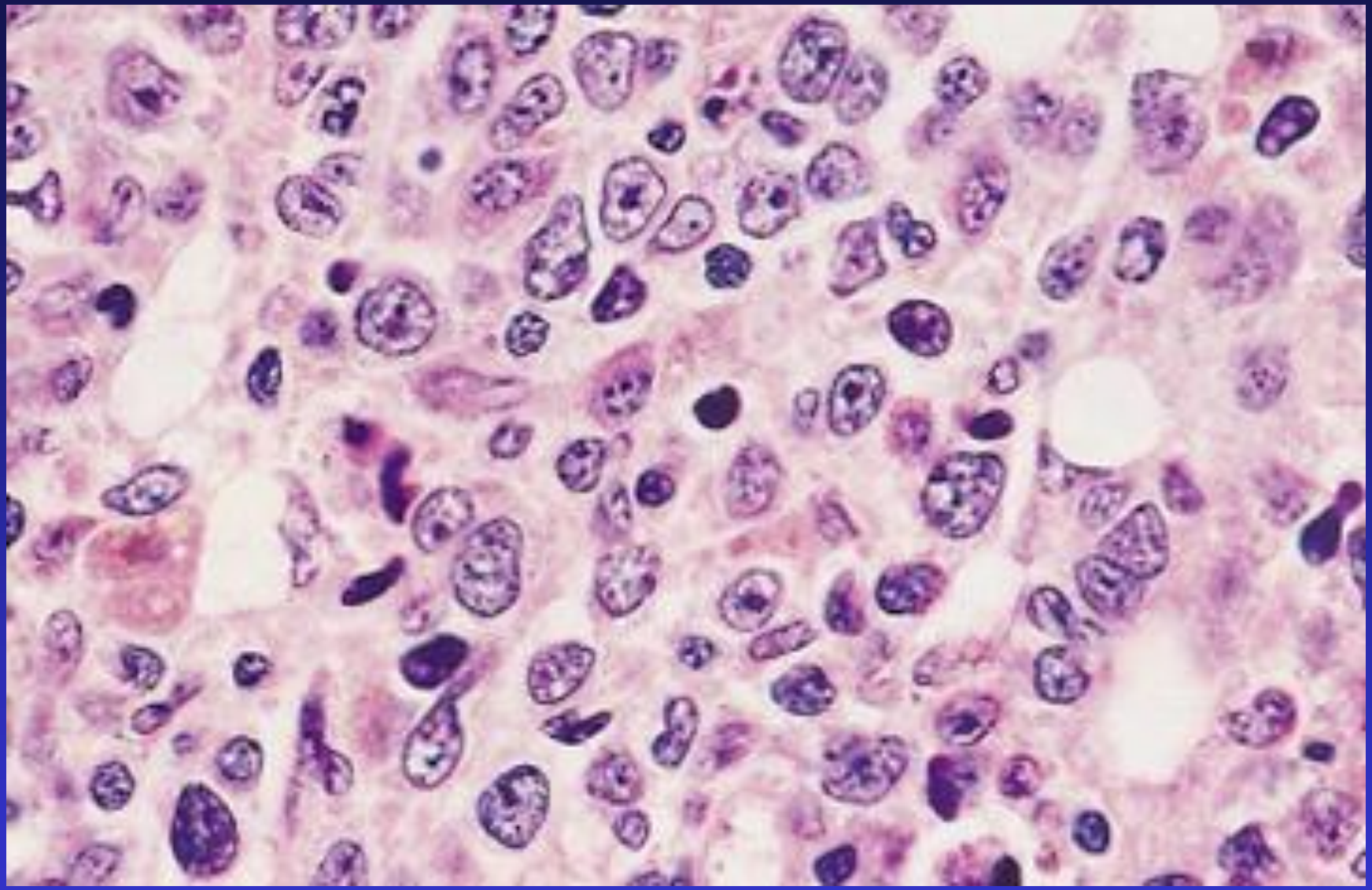


Acute basophilic leukemia: toluidine blue reaction. Maturing basophils containing metachromatic granules.

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.



Acute basophilic leukemia: trephine biopsy. Blasts and immature basophils. Scattered plasma cells, endothelial cells and macrophages with hemosiderin.

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.

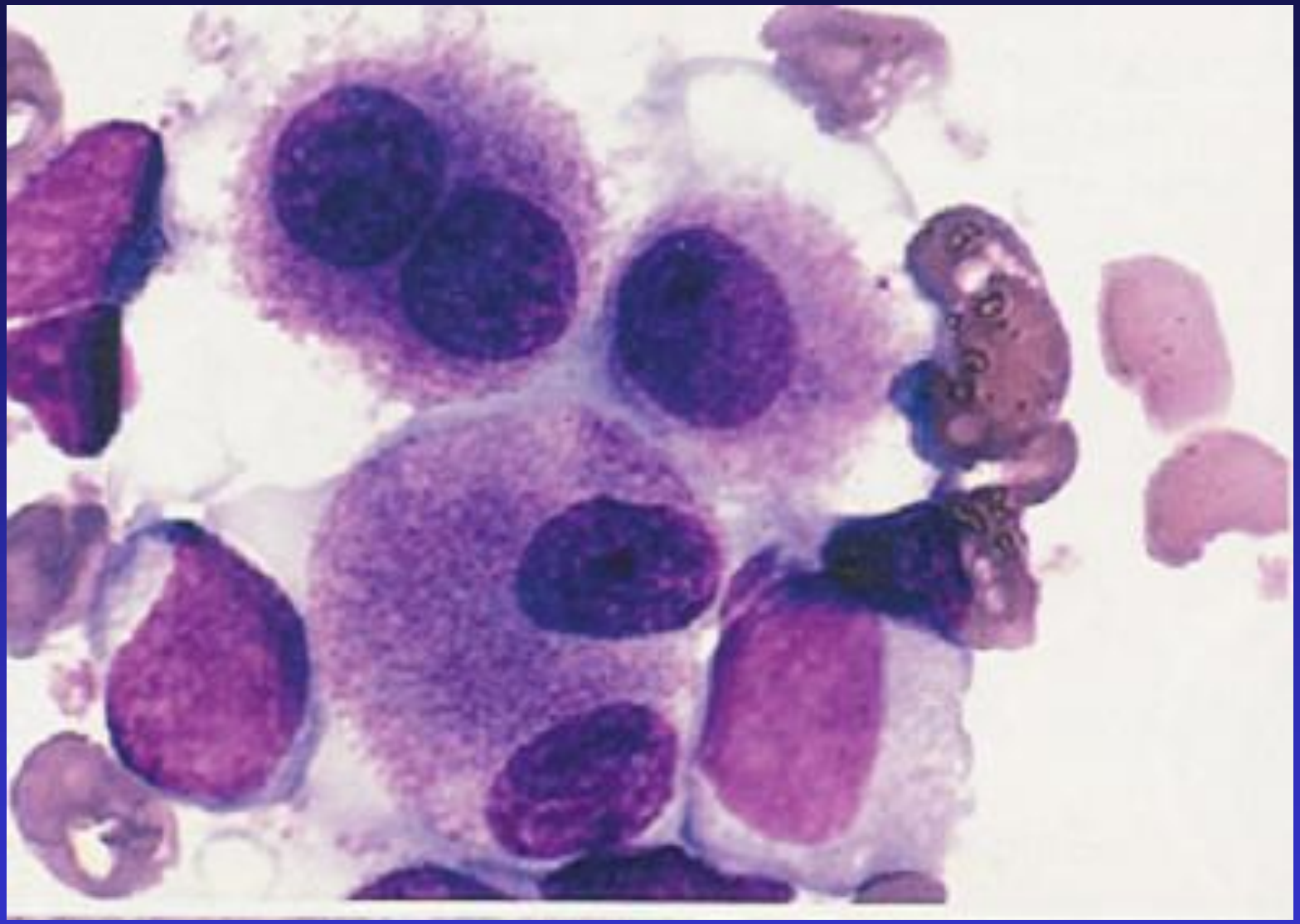
Morphology and Cytochemistry

- Marked cytopenia.
- RBCs:
  - No or minimal poikilocytosis.
  - Some anisocytosis.
  - Variable number of macrocytes.
  - Rare normoblasts.

  Ocassional 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.



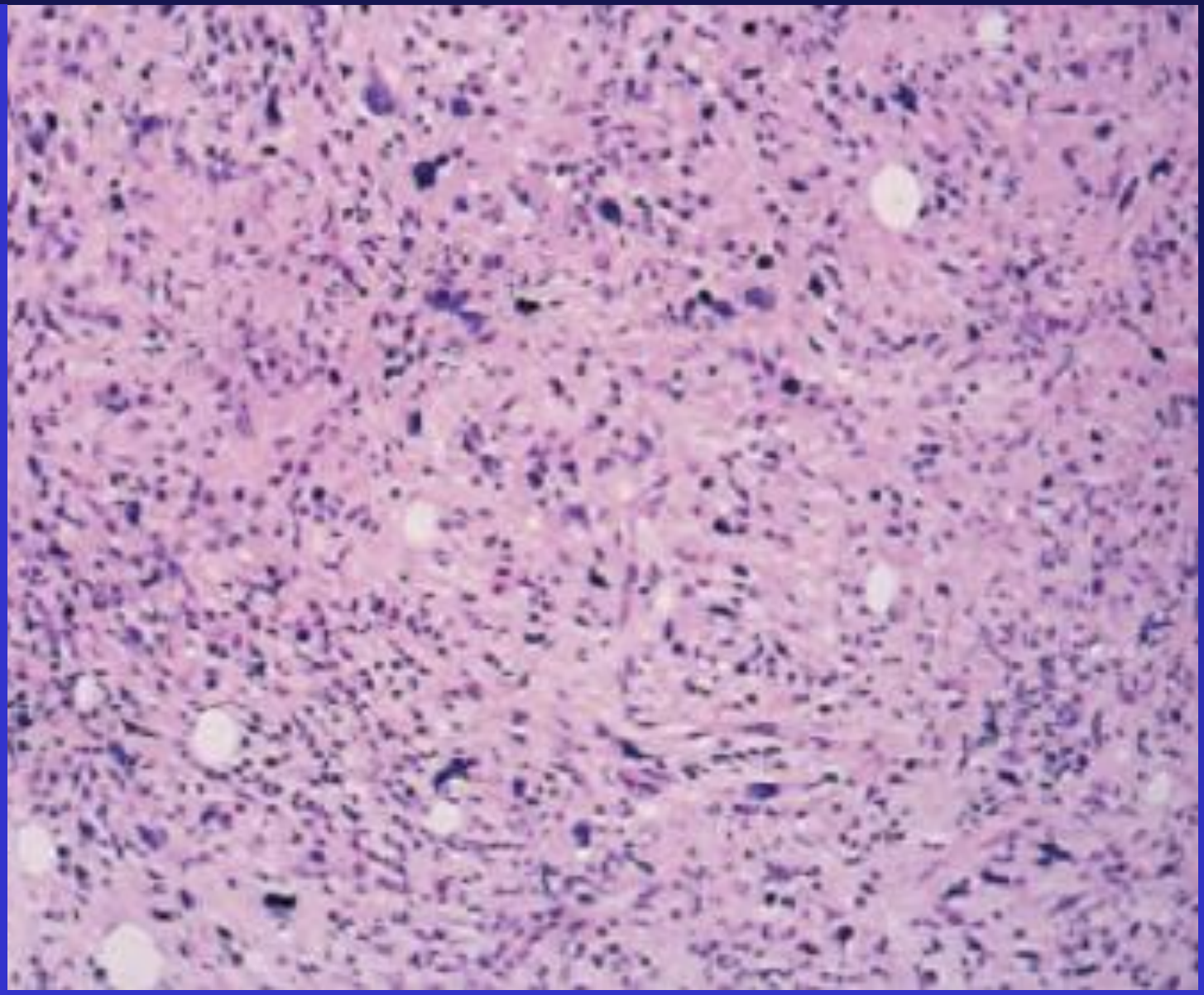
Acute myelofibrosis: trephine biopsy imprint. Several megakaryocytes with hypolobulated nuclei and blast forms.

Morphology and Cytochemistry

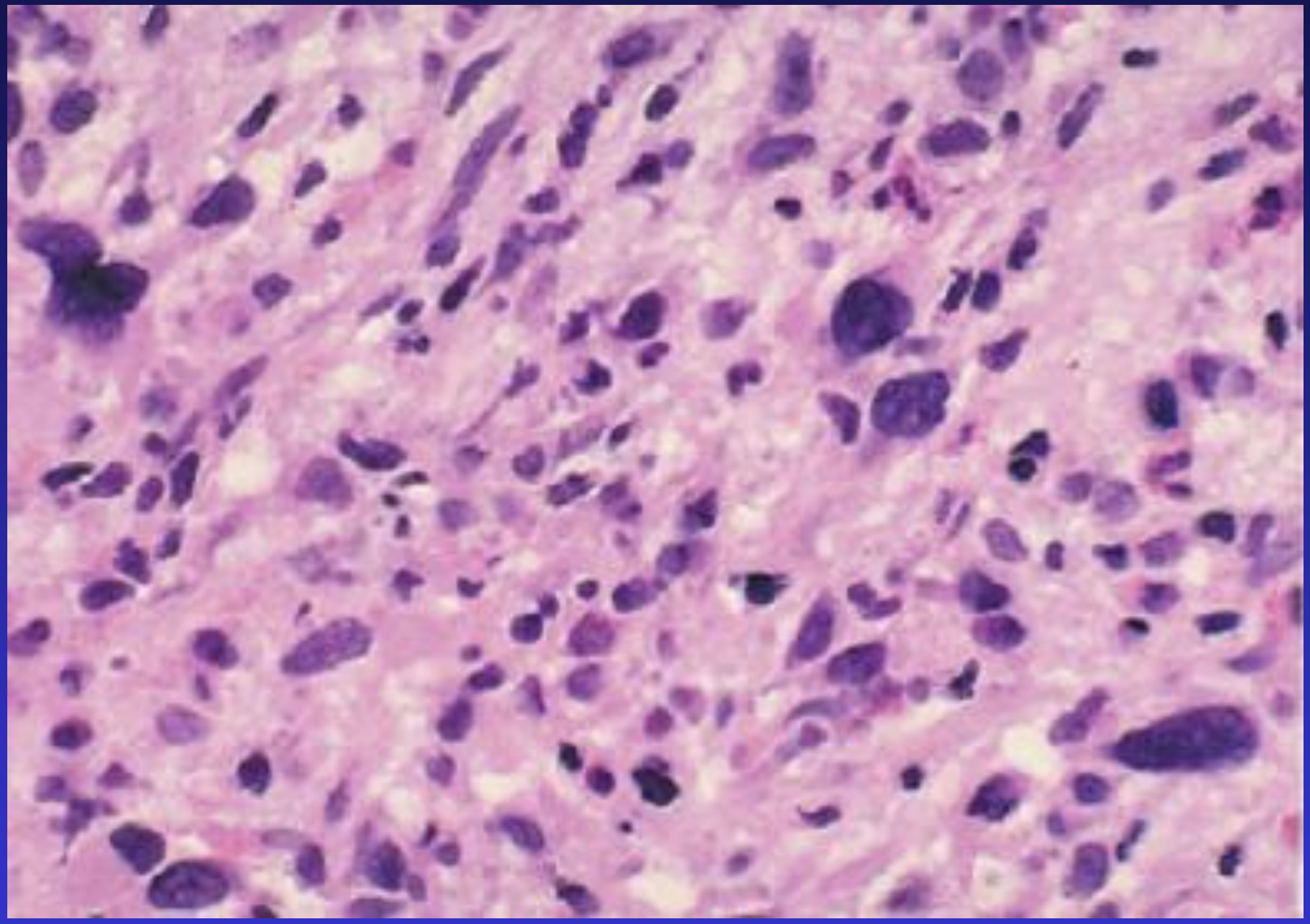
- Clusters of late erythroid precursors may be prominent.
- Conspicuous megakaryocytes, small to large with dysplastic features virtually always present.
  - Non-lobated nuclei with dispersed chromatin.
  - Uniformly eosinophilic cytoplasm, stained with PAS, FVIII, CD61.

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

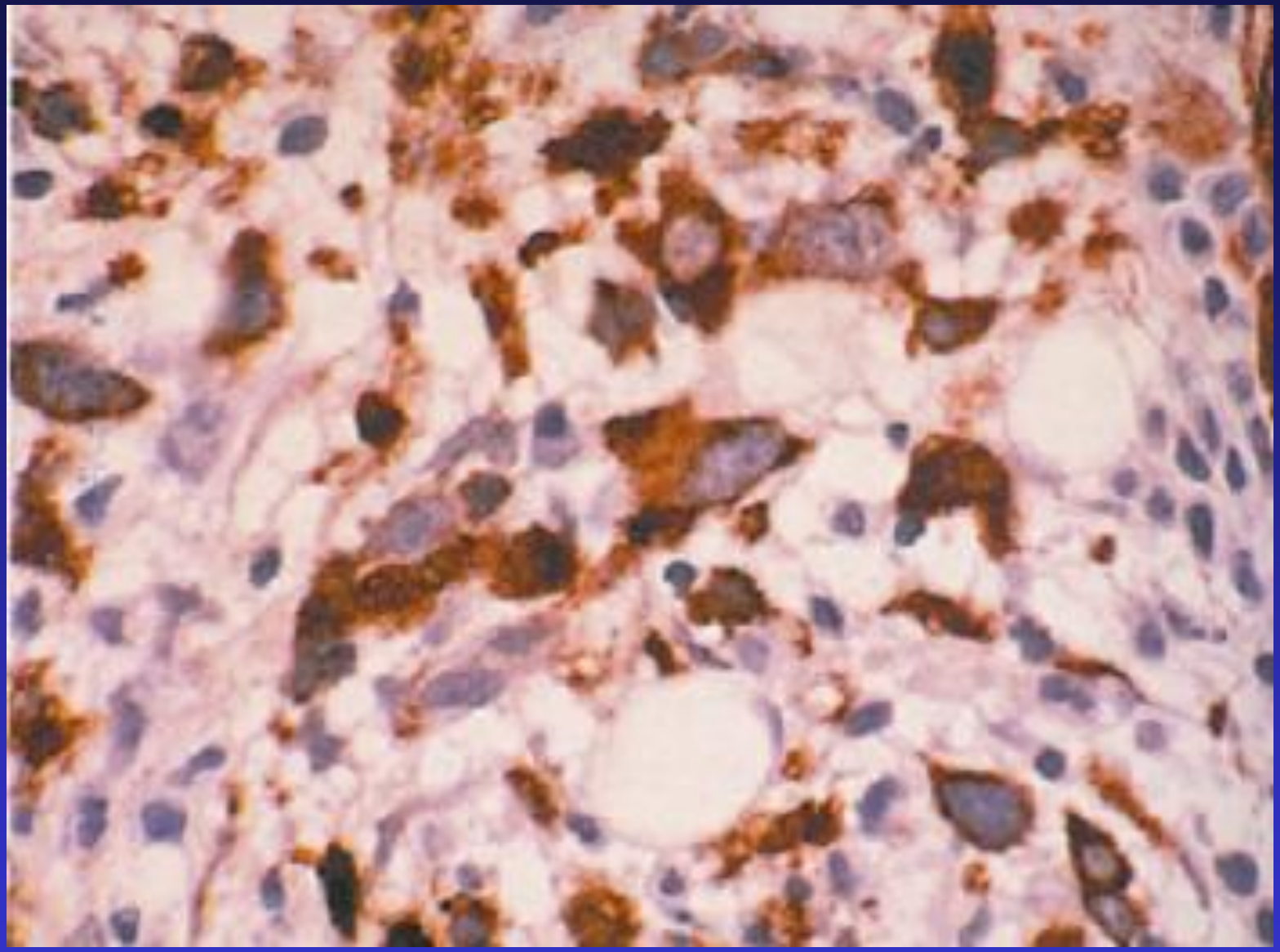
- Acute megakayoblastic leukemia.
- Acute leukemia with associated fibrosis.
- Metastatic tumor with a desmoplastic reaction.
- Chronic idiopathic myelofibrosis (CIMF).
- Distinction between acute panmyelosis with myelofibrosis, AML-M7 with fibrosis, AML with multilineage dysplasia and fibrosis may be 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, rhabdomysarcoma, 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 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

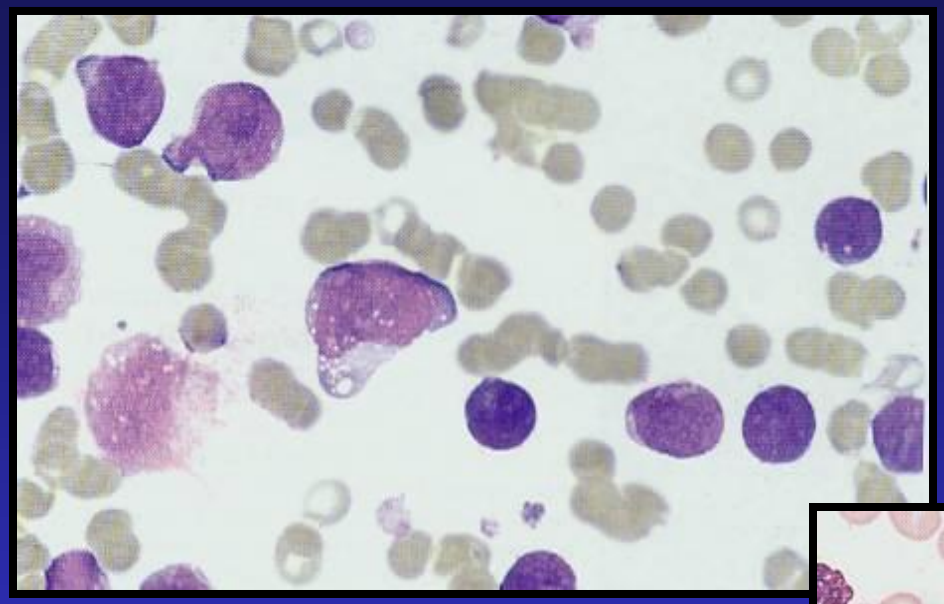
Acute Leukemias of Ambiguous Lineage

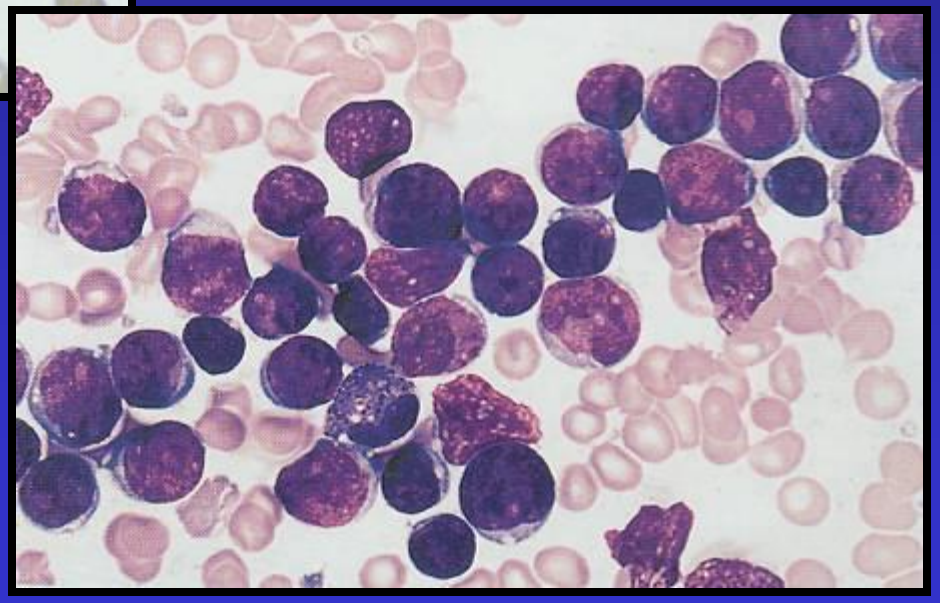
- Immunophenotype (cont)
  - Bilineal acute leukemia
    - Dual population of blasts, each with distinct lineage
      - Myeloid and lymphoid, or
      - B and T lineages
    - May evolve into biphenotypic acute leukemia

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