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Acute leukemias

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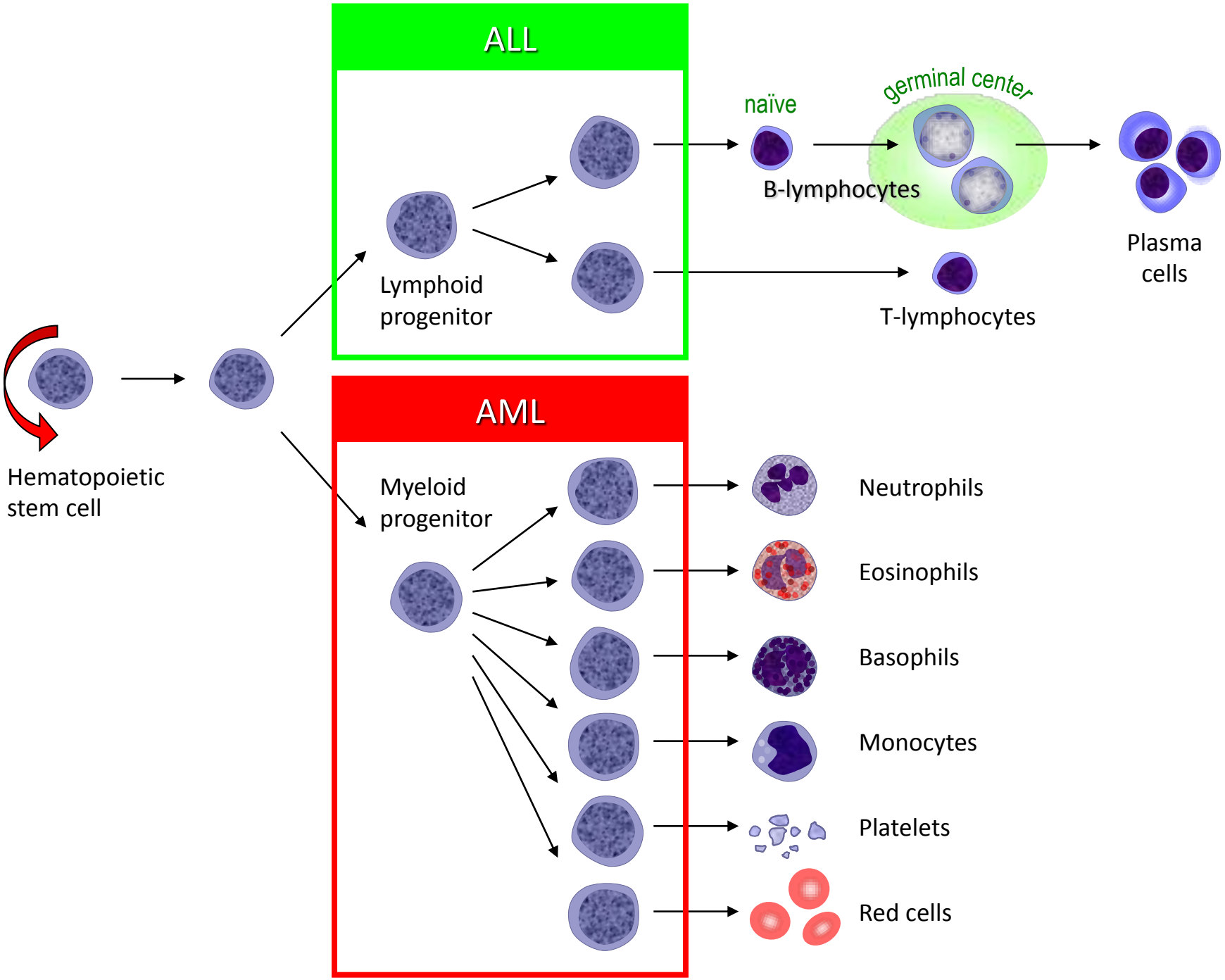
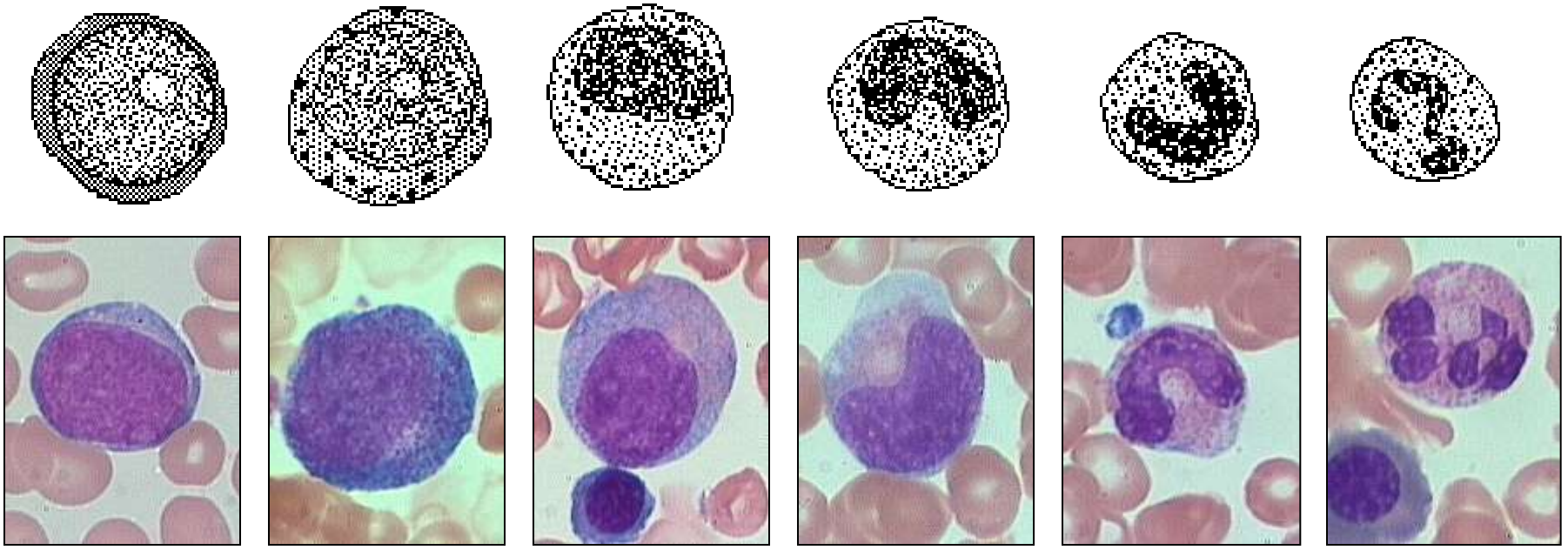
Classification of leukemias

	Acute	Chronic
Myeloid origin	Acute Myeloid Leukemia (AML)	Chronic Myeloid Leukemia (CML)
Lymphoid origin	Acute Lymphoblastic Leukemia (ALL)	Chronic Lymphocytic Leukemia (CLL)


ALL
naïve
germinal center
B-lymphocytes
Plasma cells
Lymphoid progenitor
T-lymphocytes
Hematopoietic stem cell
AML
Myeloid progenitor
Neutrophils
Eosinophils
Basophils
Monocytes
Platelets
Red cells

Myeloid maturation

myeloblast promyelocyte myelocyte metamyelocyte band neutrophil



MATURATION

Adapted and modified from U Va website

Acute myeloid leukemia (AML)

Definition

Synonyms:

- Acute myelocytic leukemia
- Acute myelogenous leukemia
- Acute nonlymphocytic leukemia

- AML describes a heterogeneous group of clonal hematopoietic progenitor cell disorders characterized by malignant neoplastic proliferation and accumulation in the bone marrow of immature and nonfunctional hematopoietic cells with a spectrum of morphologic, immunophenotypic, cytogenetic and molecular characteristics.

Epidemiology

- In adults, acute myelogenous leukemia (AML) represents about 90% of all acute leukemias.
- The incidence rises with age, occurring rarely before age 40 (<1 in 100,000), and increasing to an incidence of 16 cases per 100,000 by age 75.
- The median age at diagnosis is 65 years.

Risk factors

1. Chemicals: Exposure to benzenes, pesticides, herbicides and cigarette smoking. Exposure to chemotherapeutic agents particularly alkylating agents, topoisomerase-II inhibitors and taxanes
2. Ionizing radiation: both therapeutic and nontherapeutic
3. Genetic diseases. A higher than average incidence is seen in individuals with Down's syndrome, Klinfelter's syndrome, Ataxia telangectasia, Kostman syndrome, neurofibromatosis or Fanconi anemia.
4. Myelodysplastic syndromes or myeloproliferative disorders: there is also a greater incidence of AML in individuals with these pre-existing hematologic disorders

Pathogenesis

- AML is believed to be caused by the malignant transformation of a single hematopoietic stem cell.
- Leukemic cells are characterized by increased clonal proliferation and/or decreased cell death(apoptosis) rate with a block in normal differentiation and maturation. Effect is expansion of the neoplastic clone with a decrease in normal cells
- Leukemic transformation may occur at an early stage of hematopoiesis with the pluripotent stem cell, or, less often, with a committed stem cell.
- The pathogenesis of acute leukemia also includes a critical role for oncogenes and anti-oncogenes. About 20% to 30% of leukemia cases are associated with mutations of the RAS oncogene, the most commonly detected molecular abnormalities in AML. Control of the proliferation and differentiation of many types of cells involves RAS gene products.
- In summary, leukemogenesis appears to be a multistep process involving a susceptible hematopoietic cell, a genetic event (oncogenes, chromosomal translocations), and possibly environmental influences (chemical, radiation).

FAB Classification

- Two classification systems are used to categorize AML. The first is the classic French American British (FAB) typing classification, based on morphology and cytochemical characteristics, and immunophenotype of peripheral blood and bone marrow.
- The FAB classification defines AML as > 30% blasts in the marrow.
- It divides AML into eight subtypes.

The FAB Classification System for Acute Myelogenous Leukemia

- M0 Acute Myeloid Leukemia Without Differentiation or Maturation
- M1 Acute Myeloid Leukemia Without Maturation
- M2 Acute Myeloid Leukemia With Maturation
- M3 Acute Promyelocytic Leukemia (APL)
- M4 Acute Myelomonocytic Leukemia
- M5 Acute Monocytic Leukemia
- M6 Erythroleukemia
- M7 Acute Megakaryoblastic Leukemia

WHO Classification

- The new World Health Organization (WHO) classification defines AML as >20% blasts in the marrow or blood.
- Like the FAB classification, is based on cellular morphology, cytochemistry and immunophenotyping, but adds cytogenetic abnormalities and clinical syndromes for disease categorization. The prognostic importance of cytogenetic information supports its inclusion in this classification system.
- The WHO classification divides AML into 5 subtypes. It includes leukemias which are secondary to myelodysplastic/myeloproliferative syndromes, or to prior treatment with cytotoxic chemotherapy and/or radiotherapy.

Acute myeloid leukemia (WHO 2008)

- Acute myeloid leukemia with recurrent genetic abnormalities
  - AML with t(8;21)(q22;q22); RUNX1-RUNX1T1
  - AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11
  - APL with t(15;17)(q22;q12); PML-RARA*
  - AML with t(9;11)(p22;q23); MLLT3-MLL†
  - AML with t(6;9)(p23;q34); DEK-NUP214
  - AML with inv(3)(q21q26.2) or t(3;3)(q21;q26.2); RPN1-EVI1
  - AML (megakaryoblastic) with t(1;22)(p13;q13); RBM15-MKL1
  - Provisional entity: AML with mutated NPM1
  - Provisional entity: AML with mutated CEBPA
- Acute myeloid leukemia with myelodysplasia-related changes‡
- Therapy-related myeloid neoplasms§
- Acute myeloid leukemia, not otherwise specified (NOS)
  - Acute myeloid leukemia with minimal differentiation
  - Acute myeloid leukemia without maturation
  - Acute myeloid leukemia with maturation
  - Acute myelomonocytic leukemia
  - Acute monoblastic/monocytic leukemia
  - Acute erythroid leukemia
    - Pure erythroid leukemia
    - Erythroleukemia, erythroid/myeloid
  - Acute megakaryoblastic leukemia
  - Acute basophilic leukemia
  - Acute panmyelosis with myelofibrosis (syn.: acute myelofibrosis; acute myelosclerosis)
- Myeloid sarcoma (syn.: extramedullary myeloid tumor; granulocytic sarcoma; chloroma)
- Myeloid proliferations related to Down syndrome
  - Transient abnormal myelopoiesis (syn.: transient myeloproliferative disorder)
  - Myeloid leukemia associated with Down syndrome
- Blastic plasmacytoid dendritic cell neoplasm
- Acute leukemias of ambiguous lineage
  - Acute undifferentiated leukemia
  - Mixed phenotype acute leukemia with t(9;22)(q34;q11.2); BCR-ABL1‖
  - Mixed phenotype acute leukemia with t(v;11q23); MLL rearranged
  - Mixed phenotype acute leukemia, B/myeloid, NOS
  - Mixed phenotype acute leukemia, T/myeloid, NOS
  - Provisional entity: Natural killer (NK)–cell lymphoblastic leukemia/lymphoma

De novo and Secondary AML

- De novo AML should refer to patients with no clinical history of prior myelodysplastic syndrome, myeloproliferative disorder or exposure to potentially leukemogenic therapies or agents.
- Secondary AML should refer to patients with prior hematologic disease.

http://www.albertahealthservices.ca/hp/if-hp-cancer-guide-lyhe006-aml.pdf

History and Physical Examination

- In the history, common presenting symptoms are fatigue, easy bruising and frequent infections.
- Examination may reveal pallor and signs of hemorrhage (oral hemorrhagic bullae, petechiae, and ecchymoses).
- Chloromas
- Gingival hyperplasia, lymphadenopathy, hepatosplenomegaly, and skin infiltration (leukemia cutis) may be observed, which are more common in the monocytic subtypes of AML (FAB M4 & M5).

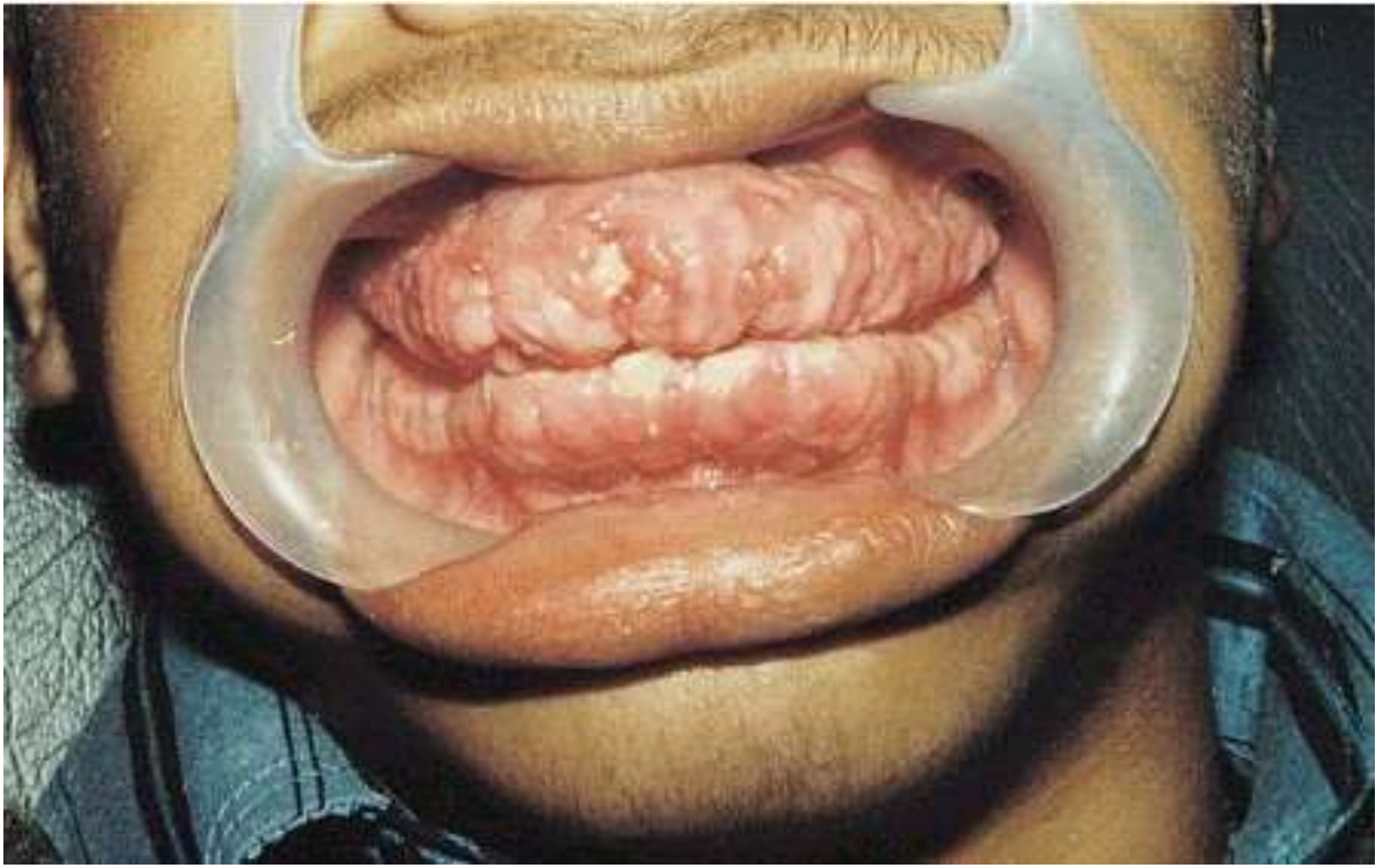
Physical Examination: Chloromas

- **Chloroma (a myeloid sarcoma) is an extramedullary manifestation of acute myeloid leukemia characterized by a solid collection of leukemic cells occurring outside of the bone marrow.**
- The term chloroma results from the greenish color of these tumors caused by the presence of myeloperoxidase.
- Chloromas may occur in virtually any organ or tissue. The most common areas of involvement are the skin (also known as leukemia cutis) and the gums.
- Skin involvement typically appears as violaceous, raised, nontender plaques or nodules, which on biopsy are found to be infiltrated with myeloblasts. Gum involvement (gingival hypertrophy) leads to swollen, sometimes painful gums which bleed easily with tooth brushing and other minor trauma.
- Other tissues which can be involved include lymph nodes, the small intestine, the mediastinum, the lung, epidural sites, the uterus, the ovaries, and the orbit of the eye.
- Central nervous system involvement, as described above, most often takes the form of meningeal leukemia, or invasion of the subarachnoid space by leukemic cells.

Physical Examination

- Hyperuricemia is the most common biochemical abnormality during treatment of acute leukemia. It generally results from the high turnover rate of the proliferating leukemic cells and can lead to urate precipitation, obstructive uropathy, and acute renal failure. All patients should receive vigorous intravenous hydration and therapy with allopurinol prior to chemotherapy.
- Tumour lysis syndrome may occur with initiation of treatment as a complication of intensive cytotoxic chemotherapy or in patients with rapidly rising or very high blast counts. This may result in potentially life-threatening metabolic complications, including hyperkalemia, hyperphosphatemia, hypocalcemia, and hyperuricemia.
- Disseminated intravascular coagulation (DIC) is common at presentation for leukemic patients, with subtype FAB M3 (acute promyelocytic leukemia). Coagulation screening is performed at initiation of workup.

Gum hypertrophy



Gum hypertrophy

Chloromas

A

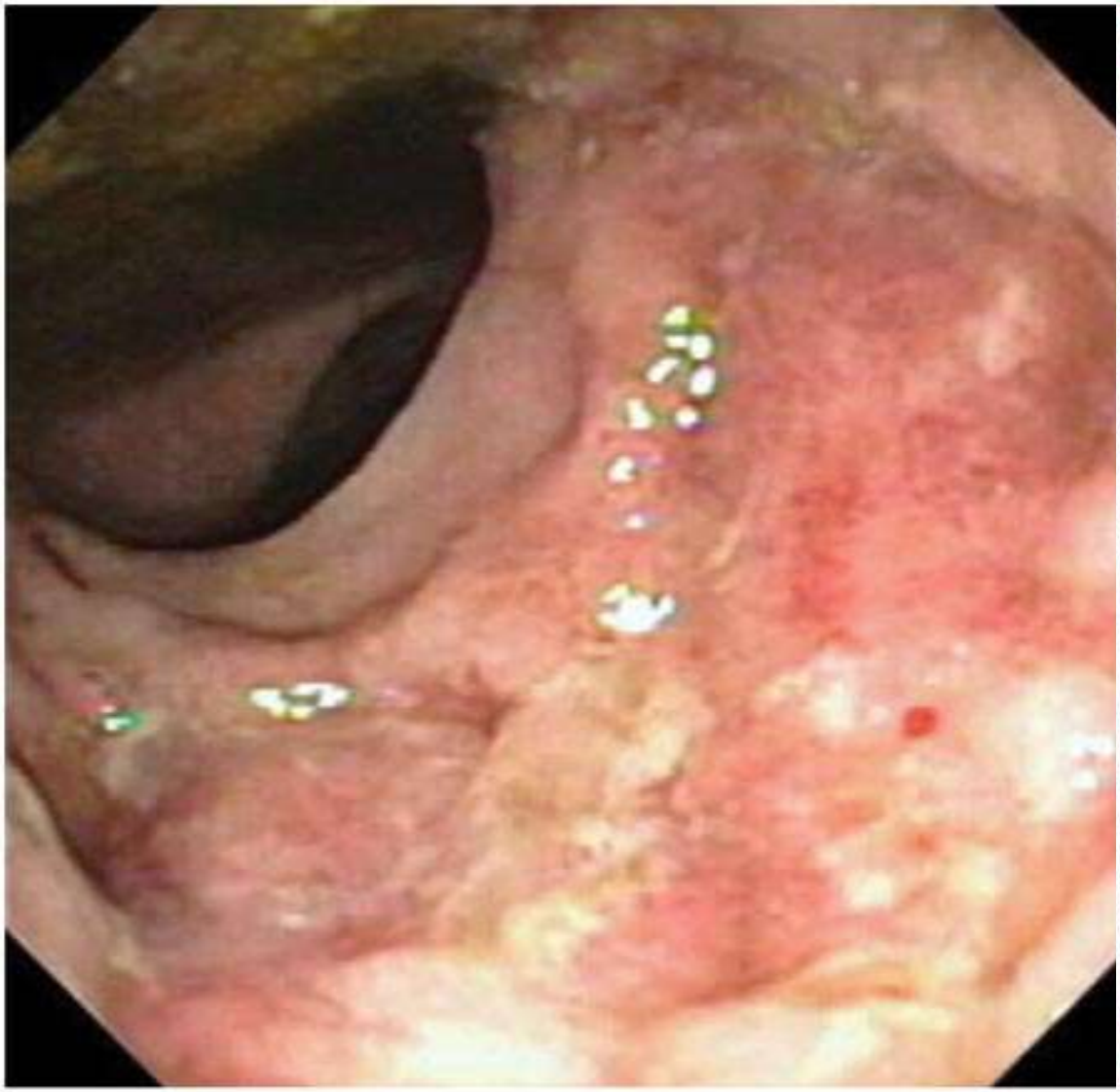
B

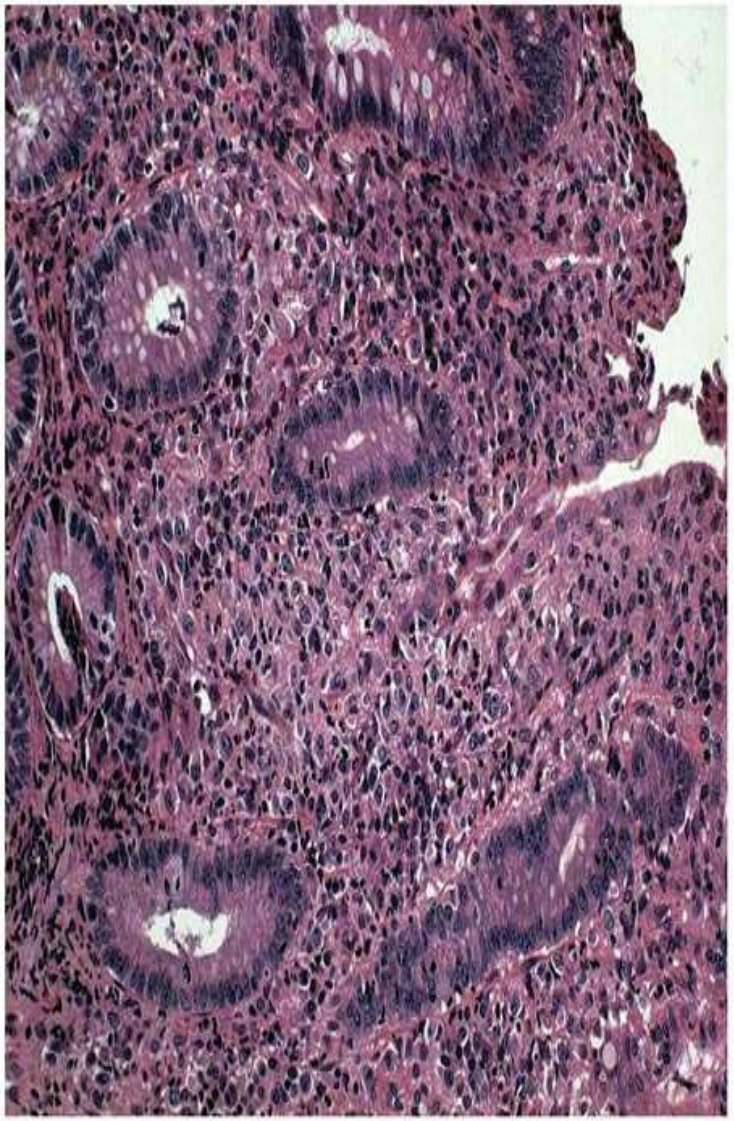
C

NEJM 1998

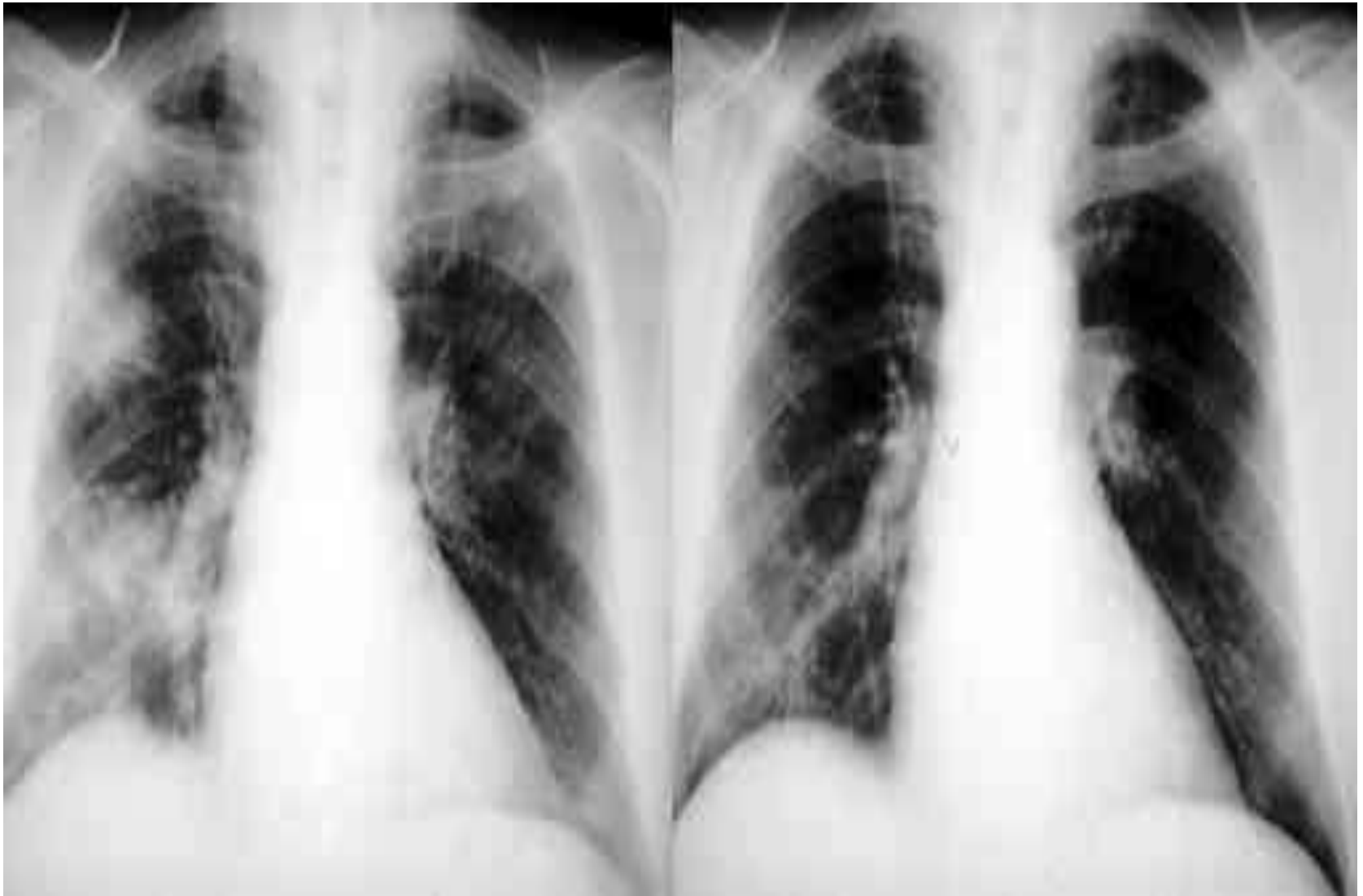
Orbital chloroma

Leukemic colitis in 75-year-old woman with AML M4





Pulmonary chloromas before and after the treatment



Hemorrhagic syndrome

Algorithm of diagnosis

- The diagnosis is often suspected and can at times be confirmed from the peripheral blood.
- All patients being considered for therapy should undergo a bone marrow aspiration and biopsy.
- Bone marrow aspiration samples should be sent for:
- *Morphology*
- *Cytochemistry*
- *Immunophenotyping*
- *Cytogenetics*

Peripheral Blood Findings 1

- **Blast forms** are nearly always present on examination of the peripheral smear. Only a small percentage of patients may present without circulating leukemic cells.
- **Hiatus leukemicus** - A condition observed in acute myelogenous leukemia in which there are numerous myeloblasts and a number of mature neutrophils in the peripheral blood, with few or no intermediate forms. The term "hiatus leukemicus" suggests a jump in cell development from an early stage to a late stage with nothing in between, analogous to changing from the appearance of a 10 year old to that of a 60 year old without any intermediate stages.
- **Auer rods** are clumps of azurophilic granular material that form elongated needles seen in the cytoplasm of leukemic blasts. They are composed of fused lysosomes and contain peroxidase, lysosomal enzymes, and large crystalline inclusions. Morphologically, the Auer "rods" come in all sizes and shapes. They have been described as needle-shapes with pointed ends (most common), comma-shapes, and diamond-shapes; others were long and rectangular. More appropriately, they can be referred to as Auer bodies.
- **Anemia and/or thrombocytopenia.** Most patients with AML present with anemia and/or thrombocytopenia.

Peripheral Blood Findings 2

- Patients may present with a total WBC which is elevated, within the normal range, or below the normal range. Five to twenty percent of patients will present with markedly elevated WBC (>100 x 10^9/L).
- **Leukemia variant according to the number of white blood cells:**

1. Leukemic that are characterized by a significant increase in the number of WBC, including leukemia cells in peripheral blood (tens or hundreds of thousands, sometimes millions in 1 /mcL of blood). This is the most common form.
2. Subleukemic – the WBC count is slightly elevated - up to 30 000 in 1 mcL of blood.
3. Aleukemic – the number of WBC is whithin the normal range and tumor cells are not present in the blood. This type is rare, but it usually occurs in the early stages of the disease.
4. Leukopenic – the number of WBC is below normal

Aspiration and biopsy of bone marrow

- Aspiration and biopsy of bone marrow, usually from the superior posterior iliac crest, is routinely performed by the hematologist to confirm the diagnosis of acute leukemia. Aspirate samples are sent for morphologic, histocytochemical, immunophenotypic, cytogenetic, and molecular analysis to enable classification of the leukemia.

The threshold number of blasts in the bone marrow is 20% or more.

- Exceptions include AML with t (8;21), inv(16) or t(15;17), in which the diagnosis of AML is made regardless of the percentage of bone marrow blasts.

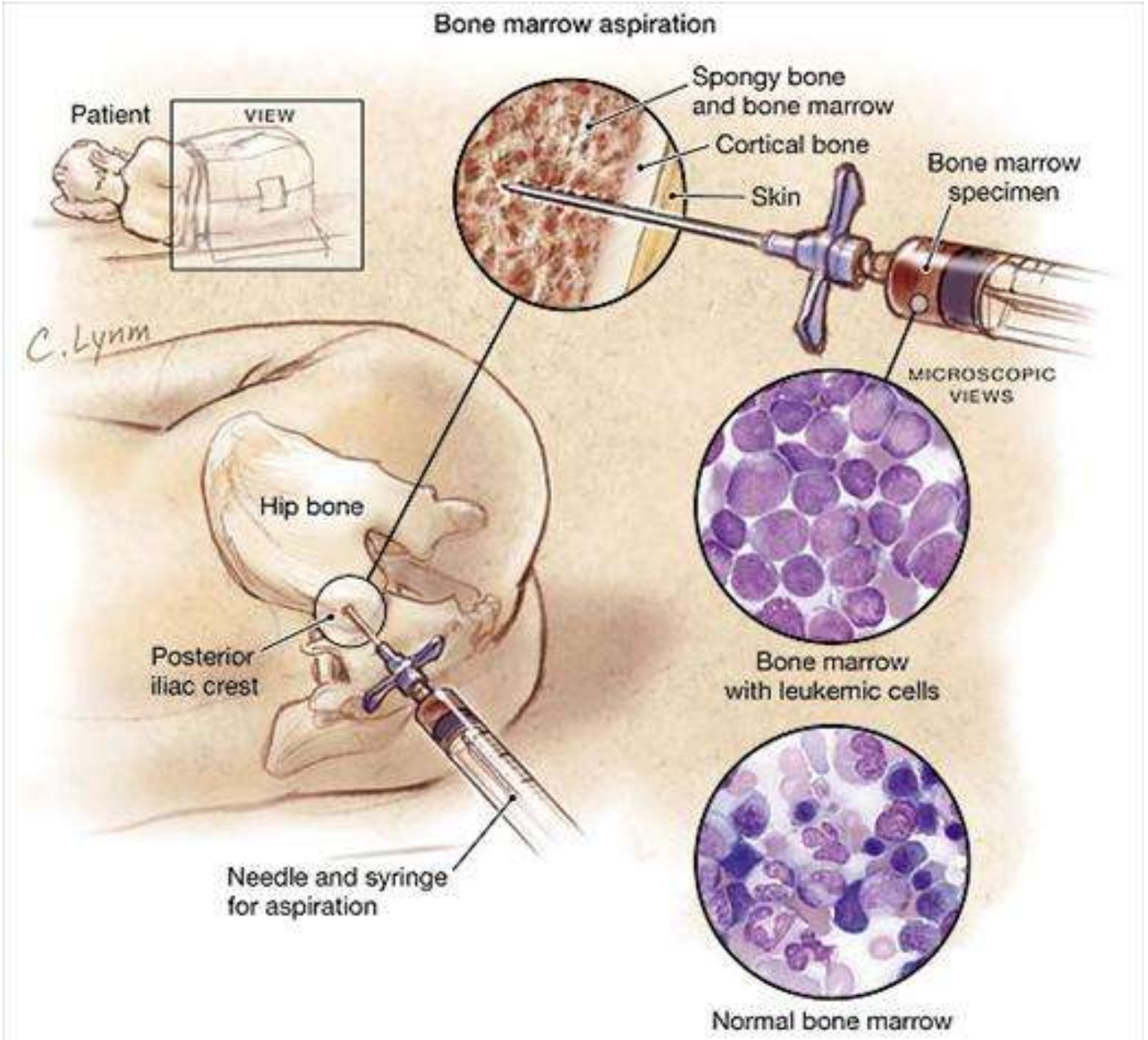


Photo credit: Mihaela Onciu, MD/ St. Jude Children's Research Hospital

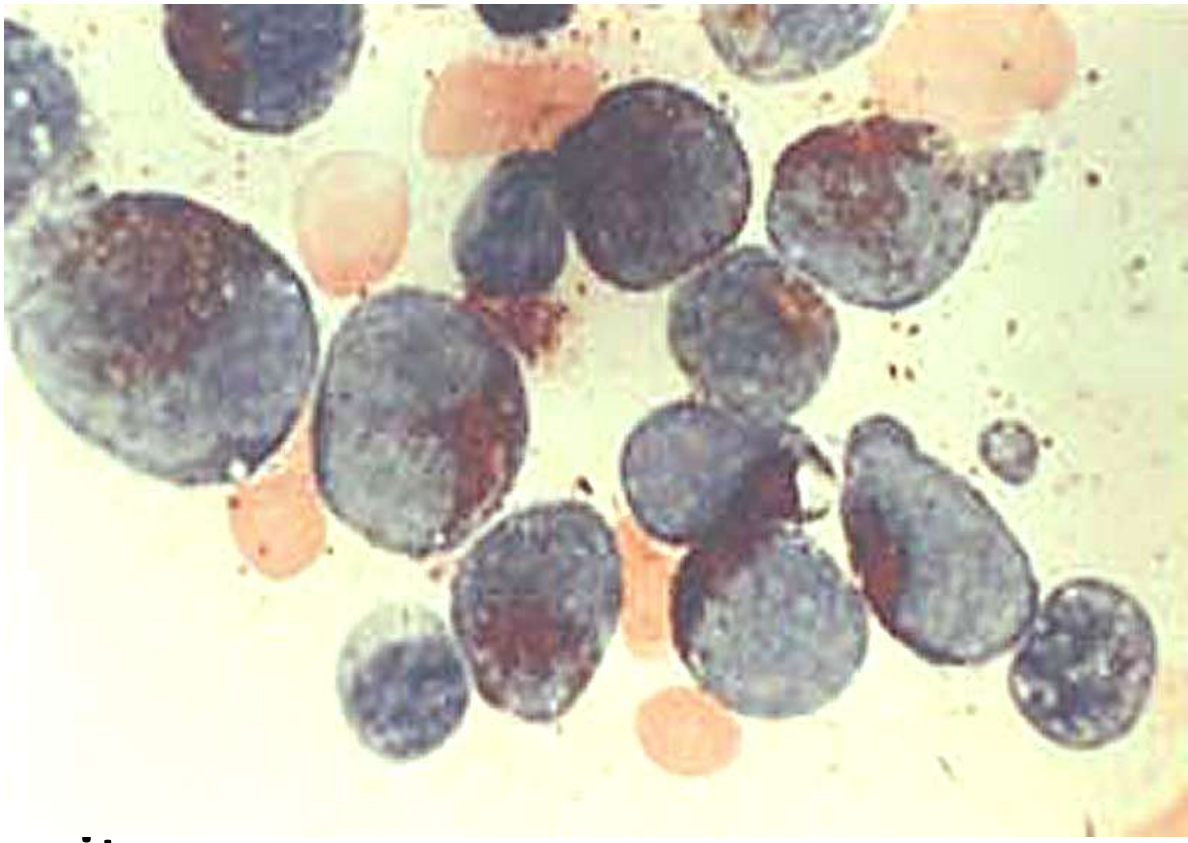
Cytochemistry

- Histocytochemical staining of bone marrow biopsy samples can distinguish myeloid from lymphoid leukemias, and may help to classify the subtypes of AML using myeloperoxidase (MPO) or Sudan black B (SBB) and nonspecific esterase (NSE) stains.
- Detection of MPO (if present in ≥ 3% of blasts) indicates myeloid differentiation, but its absence does not exclude a myeloid lineage because early myeloblasts and monoblasts may lack MPO.
- SBB staining parallels MPO but is less specific.
- NSE stains show diffuse cytoplasmic activity in monoblasts (usually > 80% positive) and monocytes (usually > 20% positive)

Myeloperoxidase

(MPO)

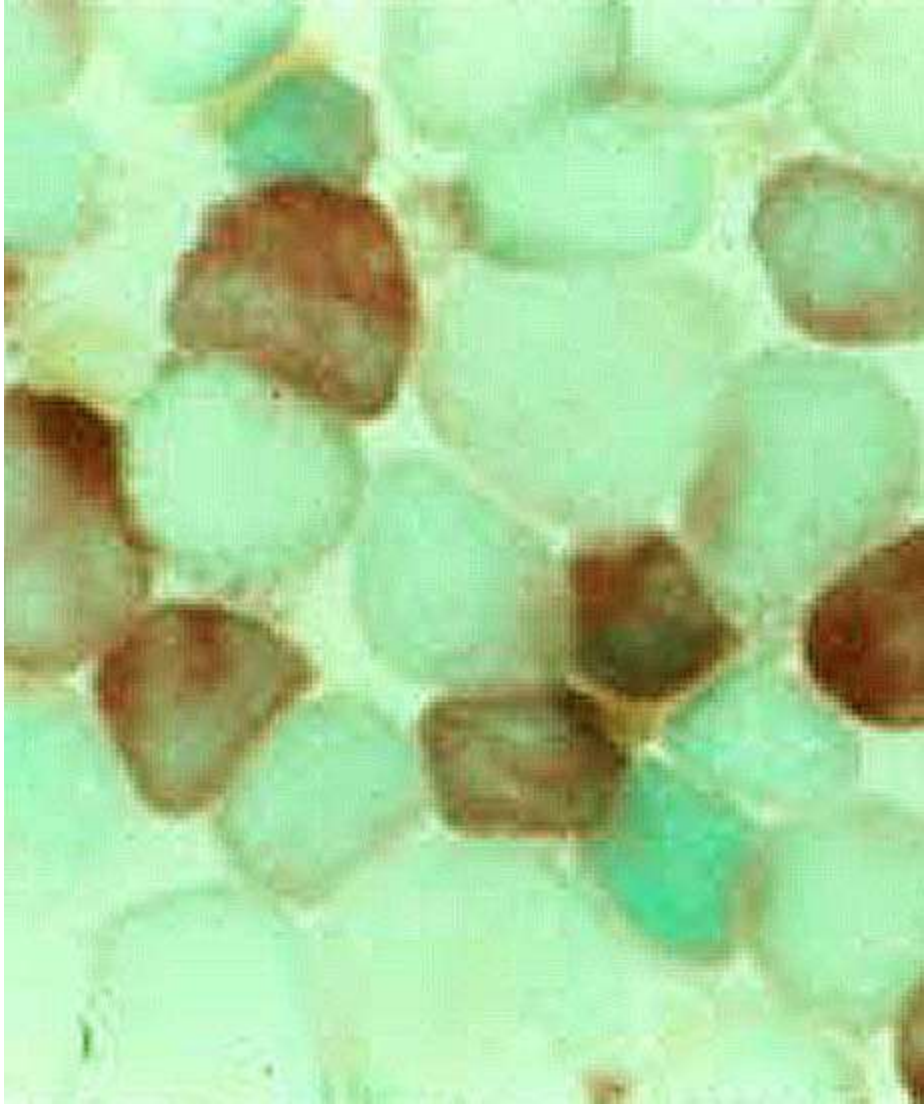
Brown black deposits



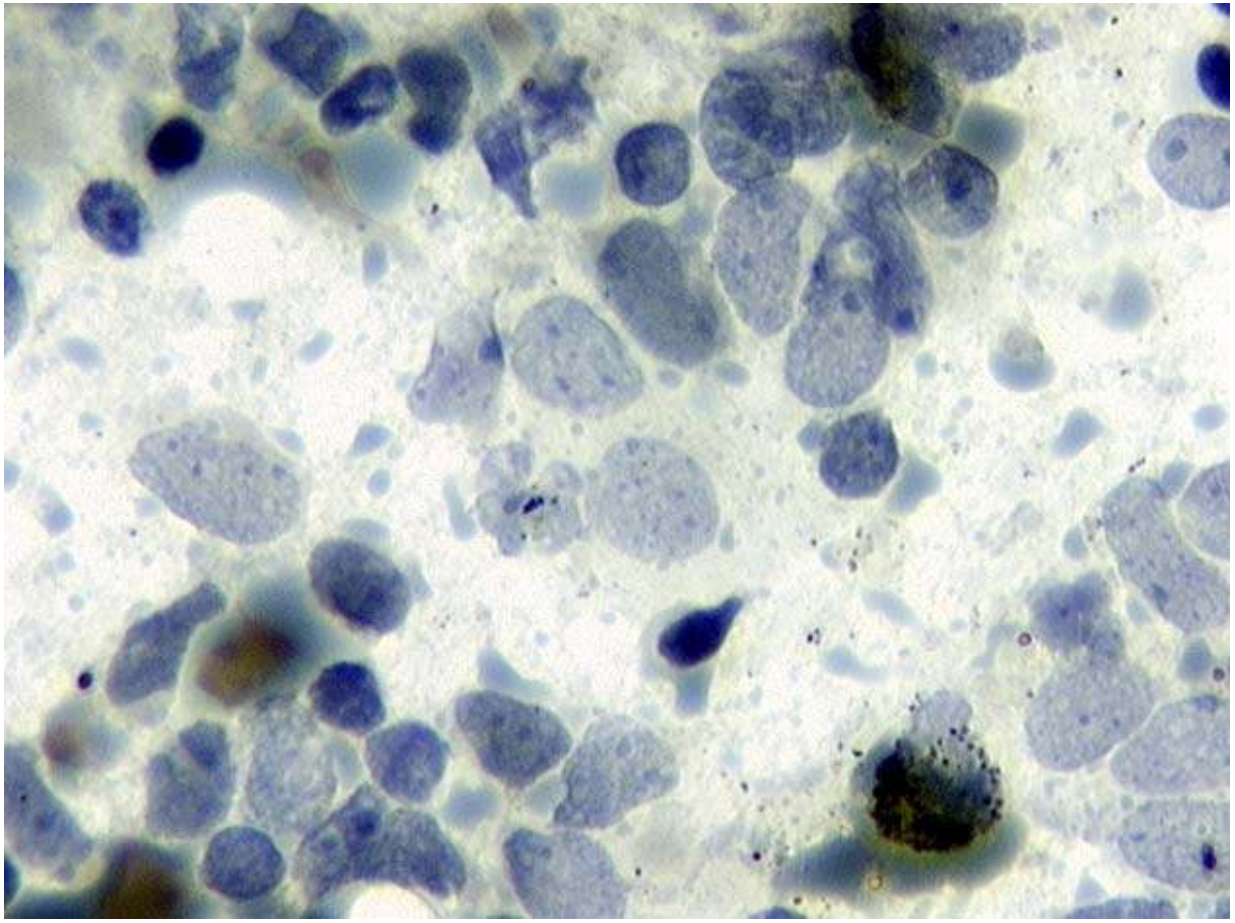
Non-Specific Esterase

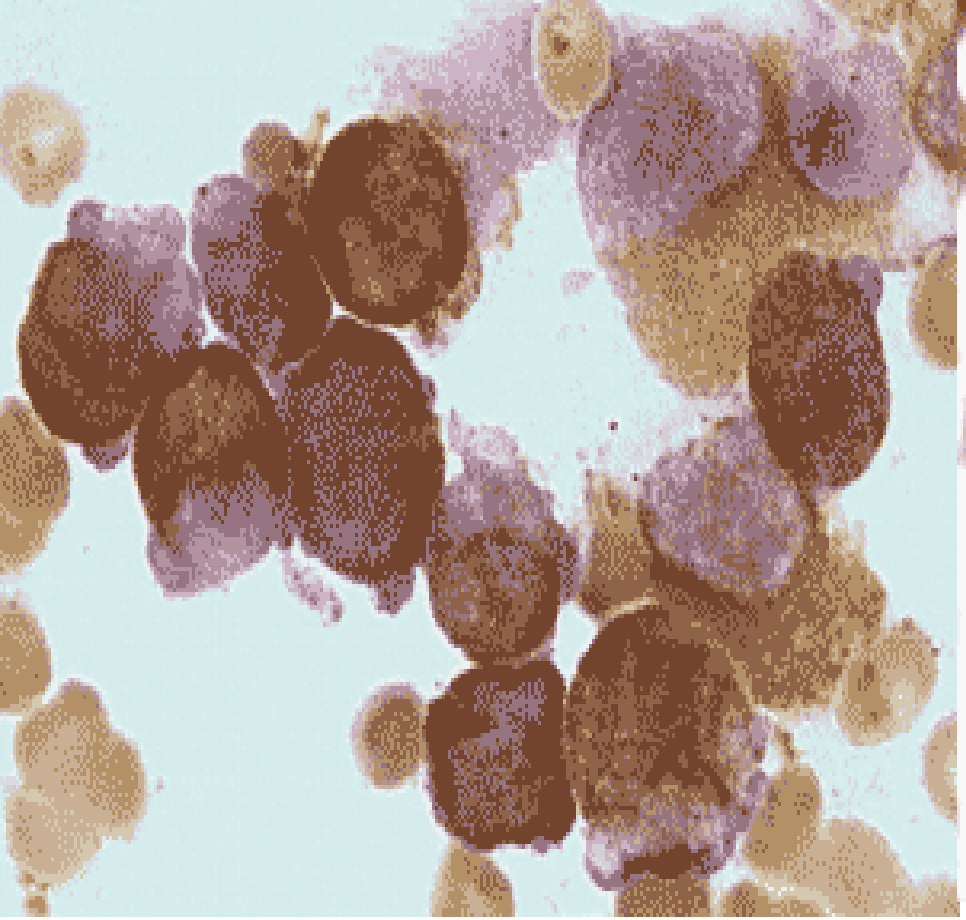
Monocytic Line

Brown deposits



- SUDAN BLACK B





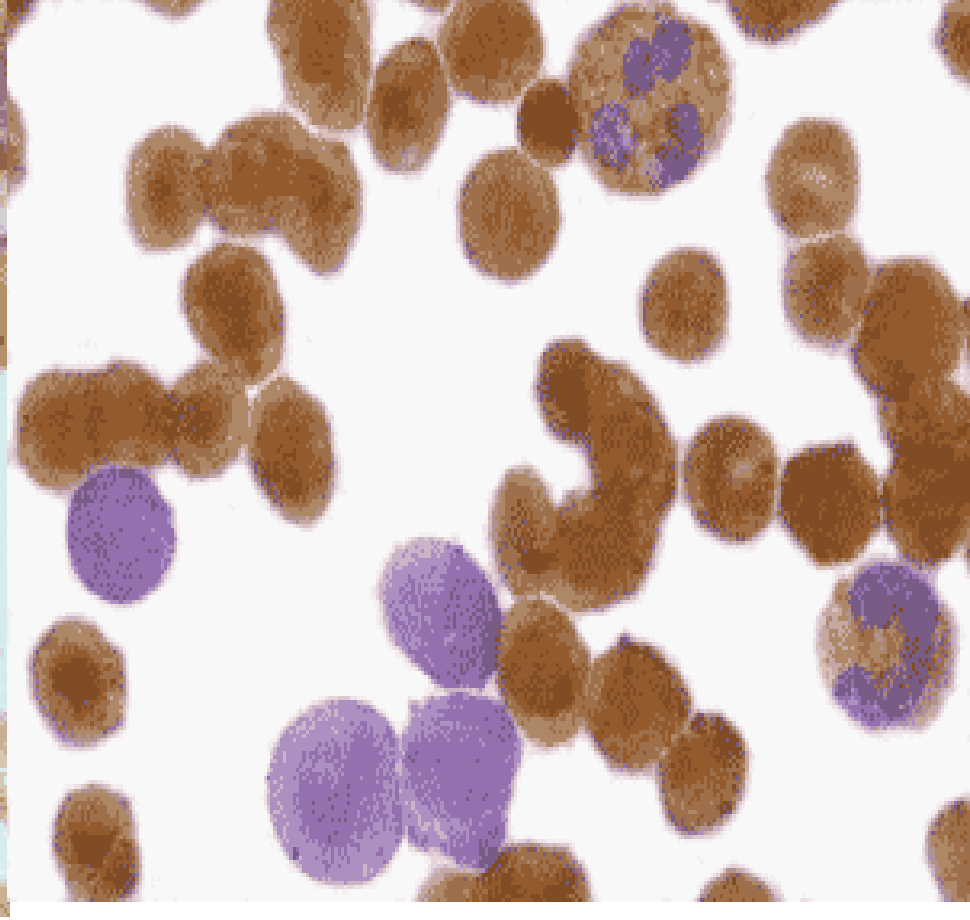
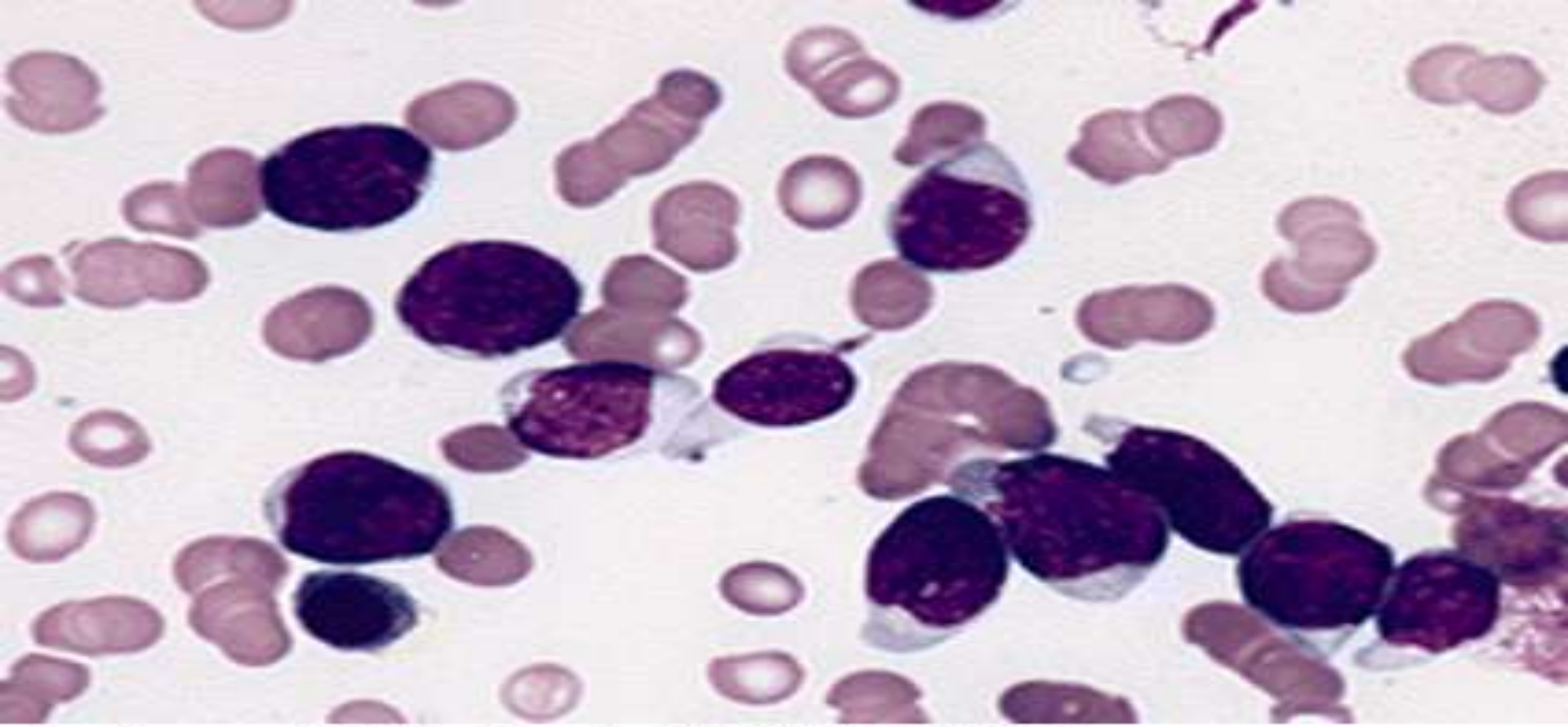
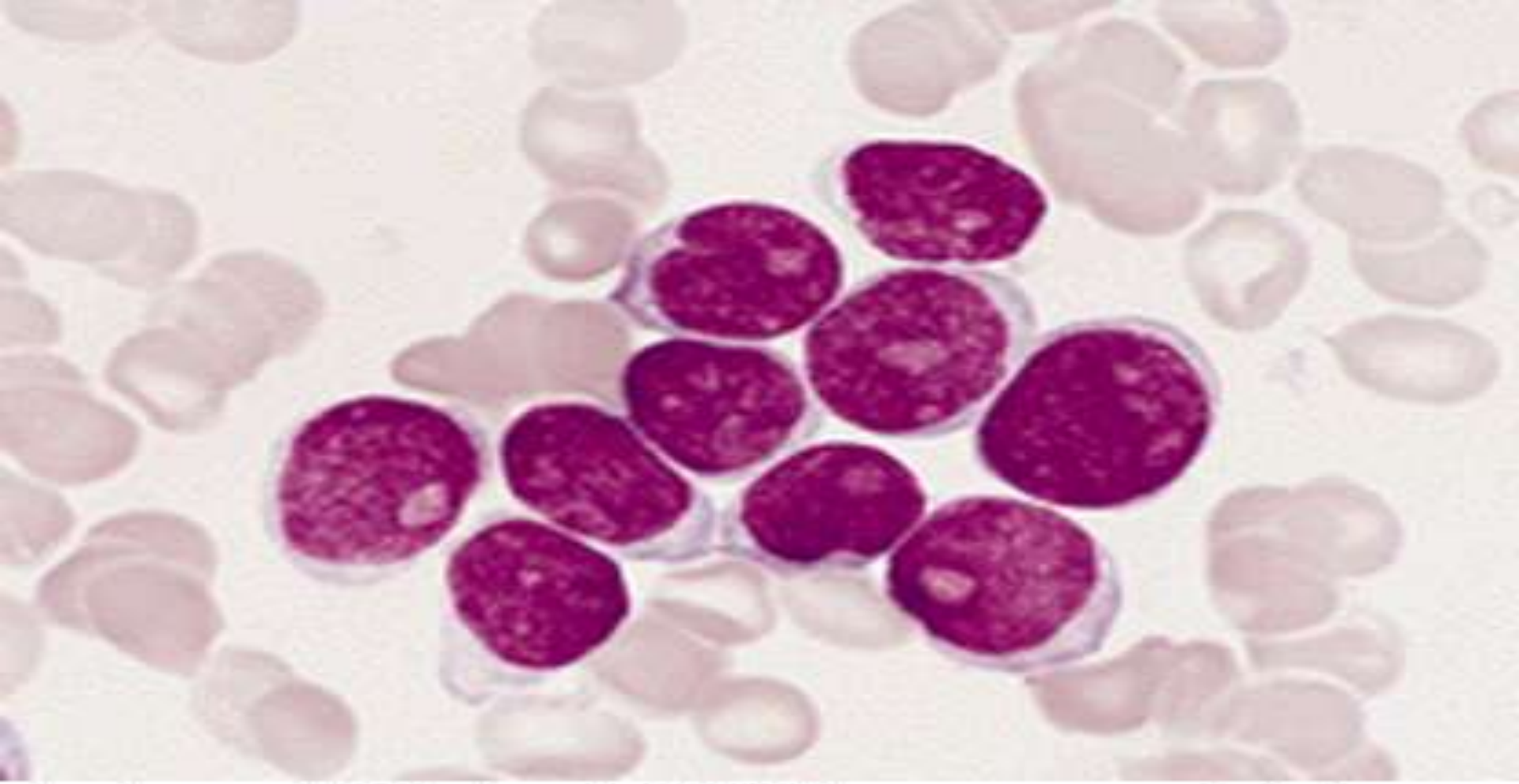


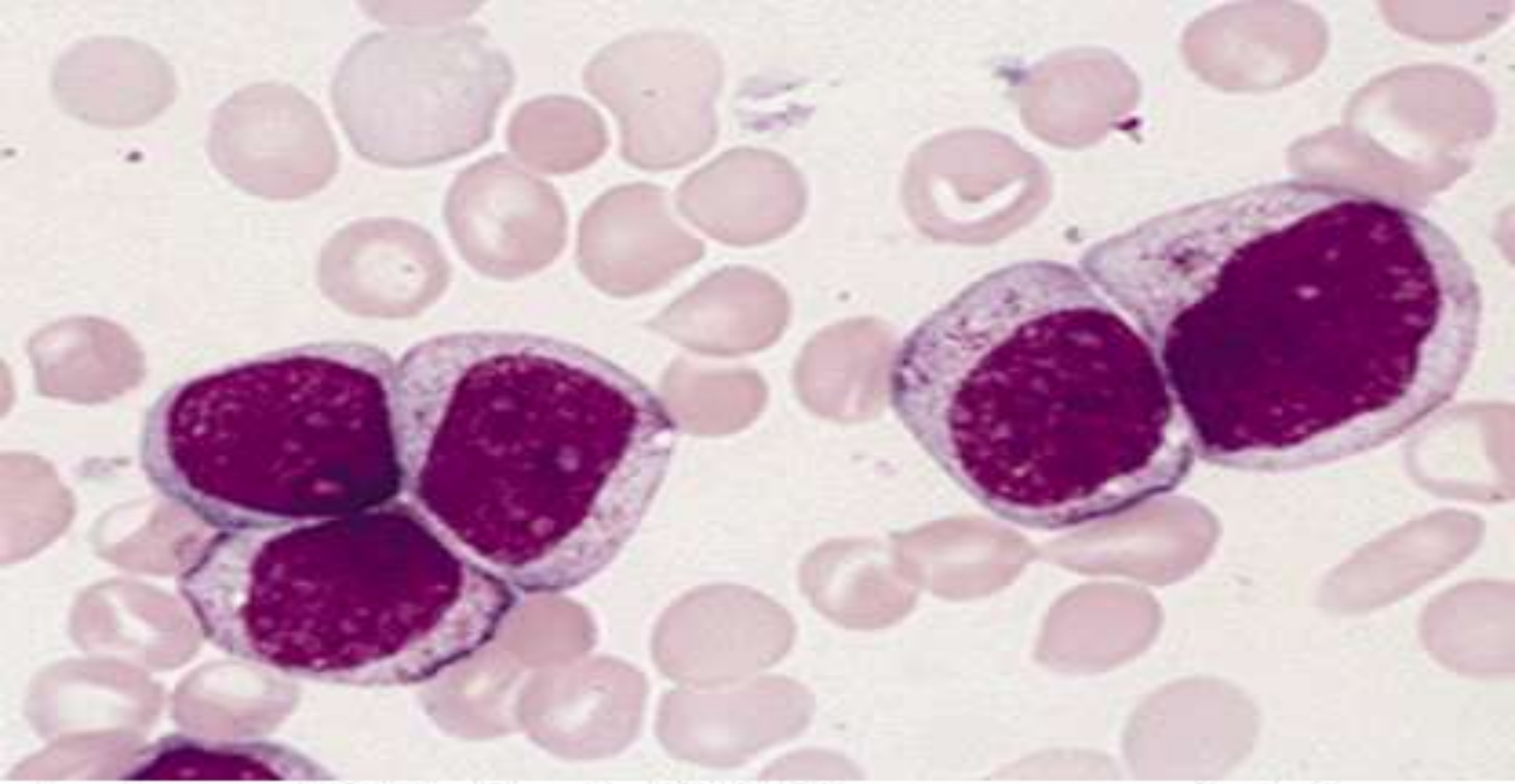
Fig. 1. Positive for MPO blasts (M3) (bone marrow).
Fig. 2. Positive for MPO in neutrophils and negative in blasts in ALL (L2).



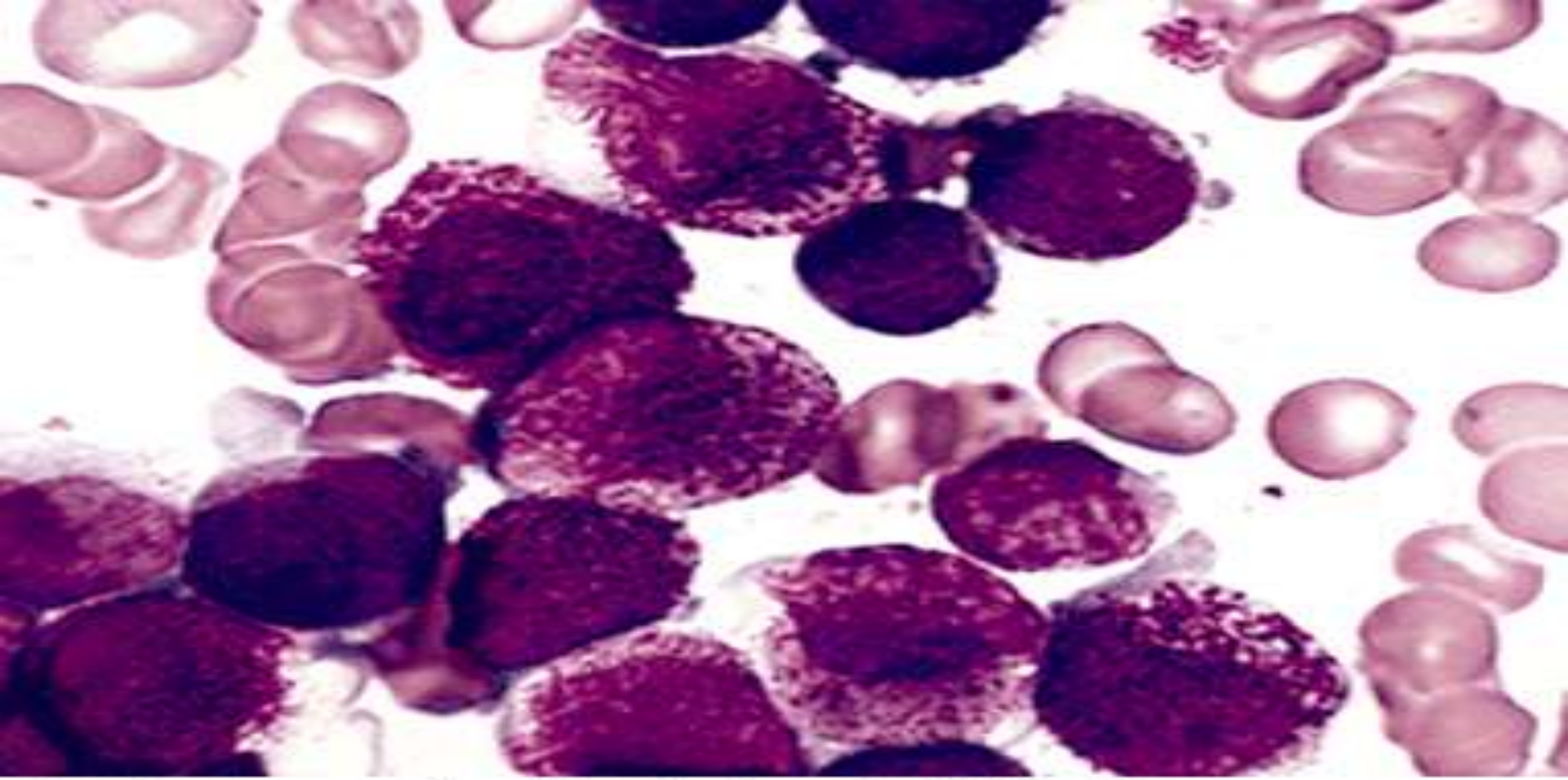
Acute myeloid leukemia (AML FAB M0) Bone marrow aspirate from a patient with AML (FAB classification M0). (Wright-Giemsa stain). The blasts lack differentiating features and were nonreactive to Sudan Black B and myeloperoxidase staining. More than 20 percent of the blasts expressed myeloid antigens CD13 and CD33. The blasts were terminal transferase negative and nonreactive with antibodies to lymphocytes. Auer rods were not found. (From Brunning, RD, McKenna, RW. Tumors of the bone marrow. Atlas of tumor pathology (electronic fascicle), Third series, fascicle 9, 1994, Washington, DC. Armed Forces Institute of Pathology.)



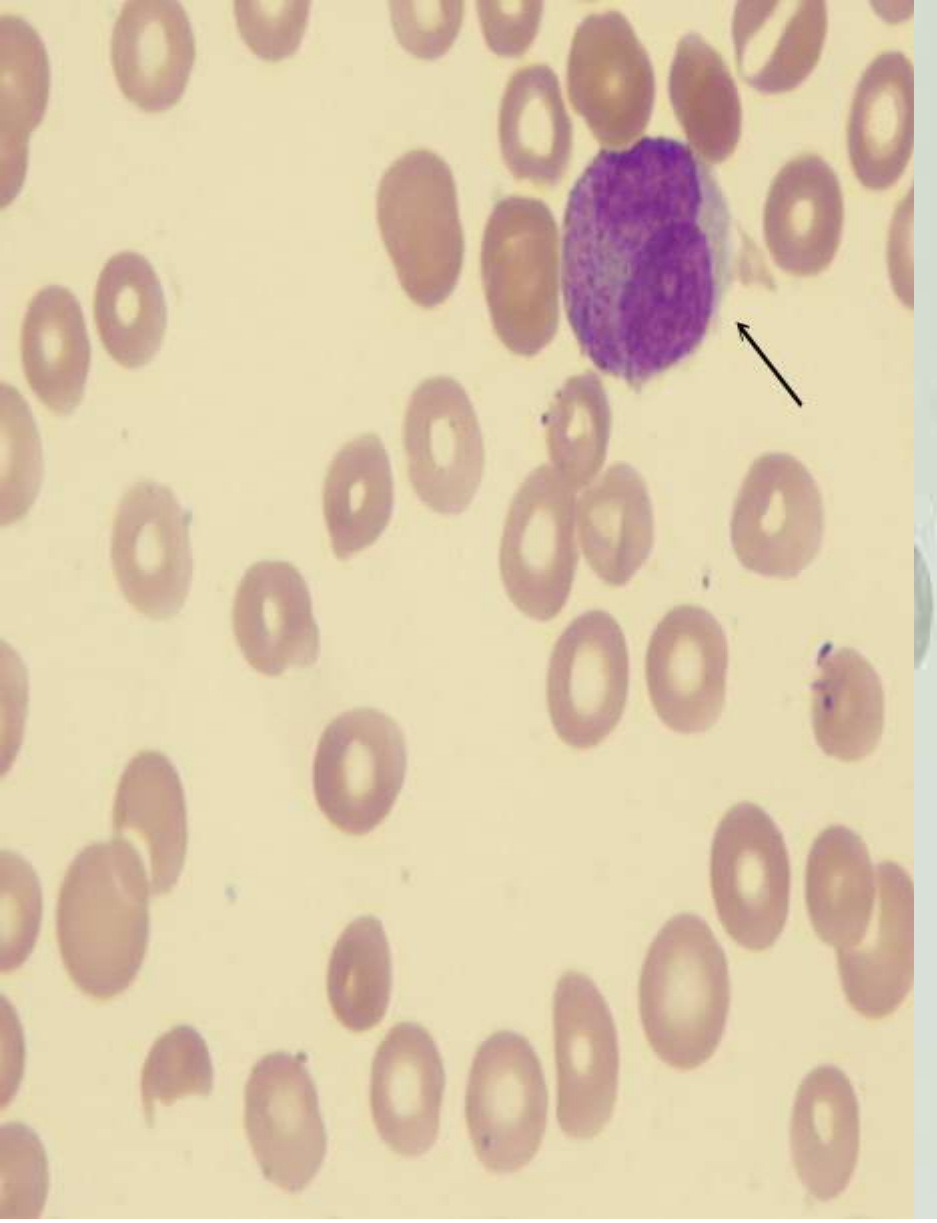
Acute myeloid leukemia (M1) Bone marrow aspirate from a patient with AML (FAB classification M1). (Wright-Giemsa stain). The majority of cells have a rim of pale to slightly basophilic agranular cytoplasm. The nuclei have finely dispersed chromatin and prominent nucleoli. (From Brunning, RD, McKenna, RW. Tumors of the bone marrow. Atlas of tumor pathology (electronic fascicle), Third series, fascicle 9, 1994, Washington, DC. Armed Forces Institute of Pathology.)

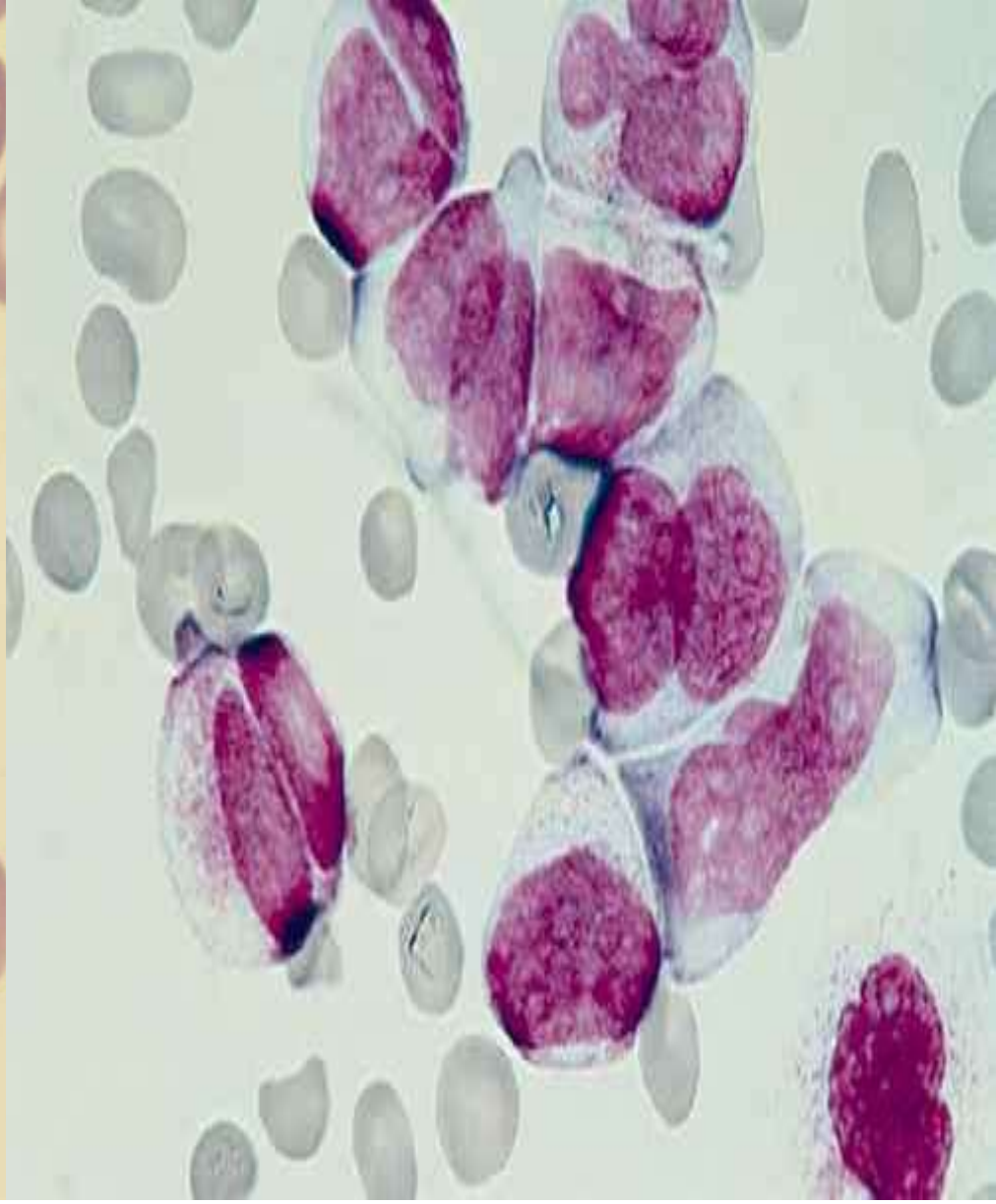


Acute myeloid leukemia (M2) Bone marrow aspirate from a patient with AML (FAB classification M2). (Wright-Giemsa stain). The WBC count was 70,000/μL and was comprised almost entirely of myeloblasts with numerous azurophilic granules. (From Brunning, RD, McKenna, RW. Tumors of the bone marrow. Atlas of tumor pathology (electronic fascicle), Third series, fascicle 9, 1994, Washington, DC. Armed Forces Institute of Pathology.)

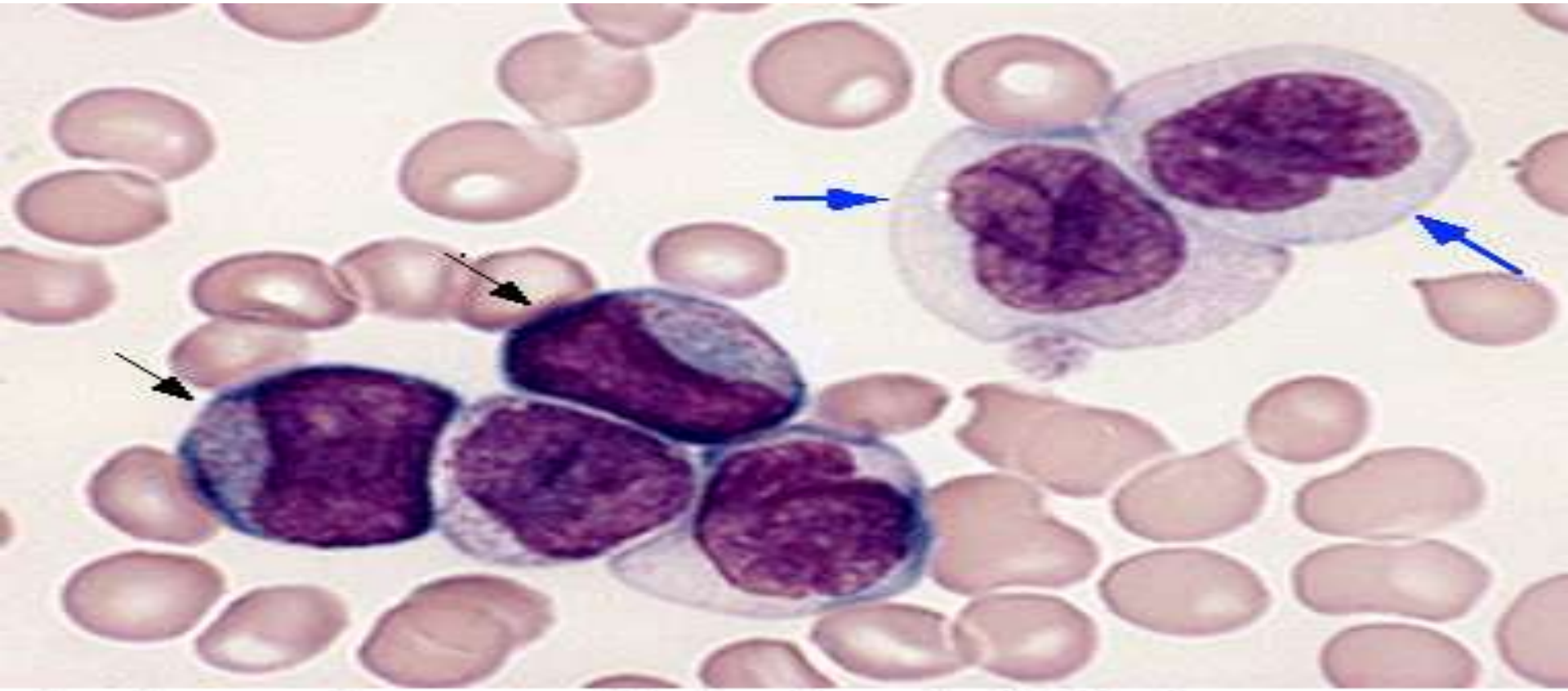


Acute promyelocytic leukemia (M3) Bone marrow aspirate from a patient with the hypergranular promyelocytic variant of AML (FAB classification M3). (Wright-Giemsa stain). The cytoplasm of the majority of promyelocytes contains abundant azurophilic granulation. (From Brunning, RD, McKenna, RW. Tumors of the bone marrow. Atlas of tumor pathology (electronic fascicle), Third series, fascicle 9, 1994, Washington, DC. Armed Forces Institute of Pathology.)

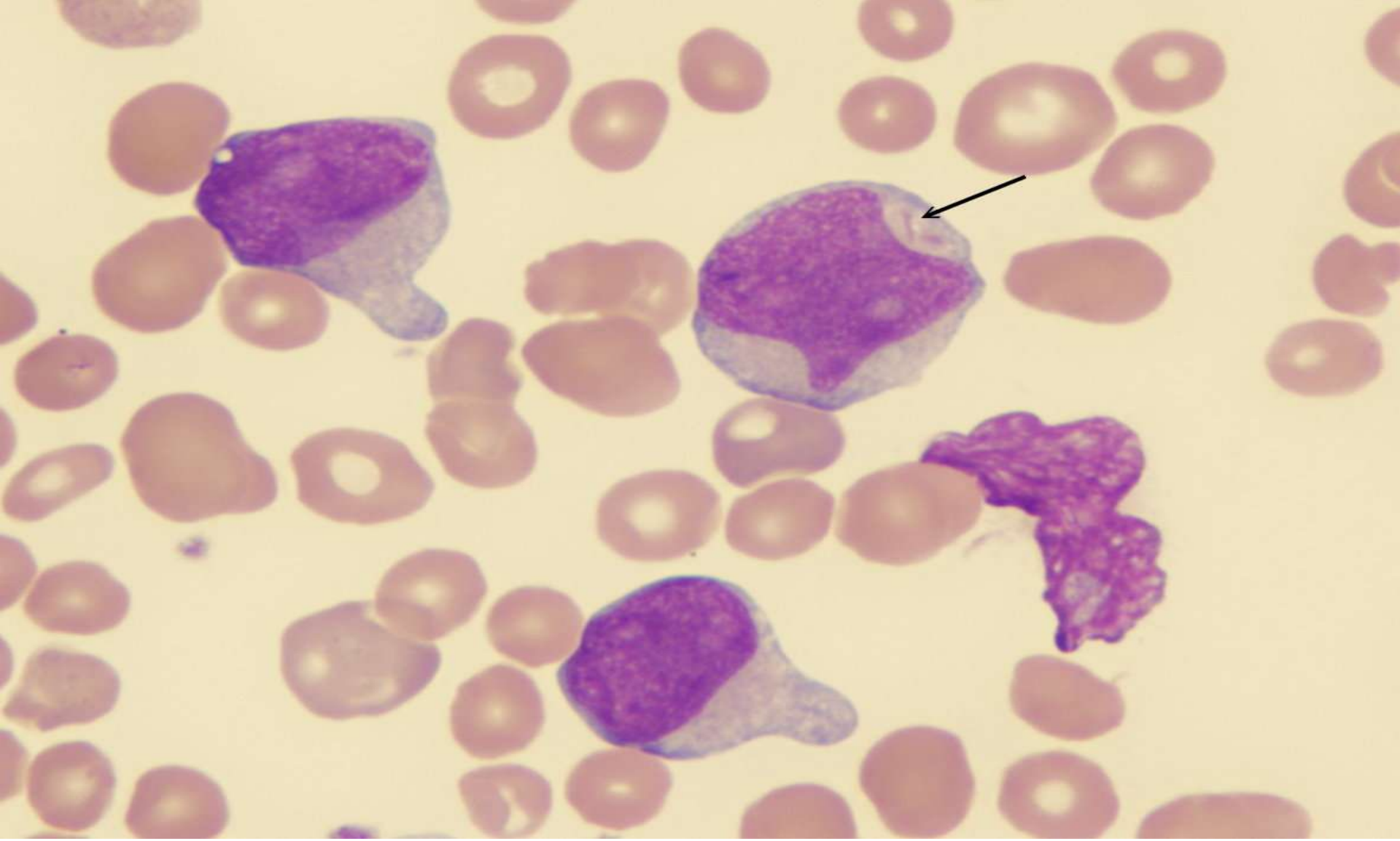




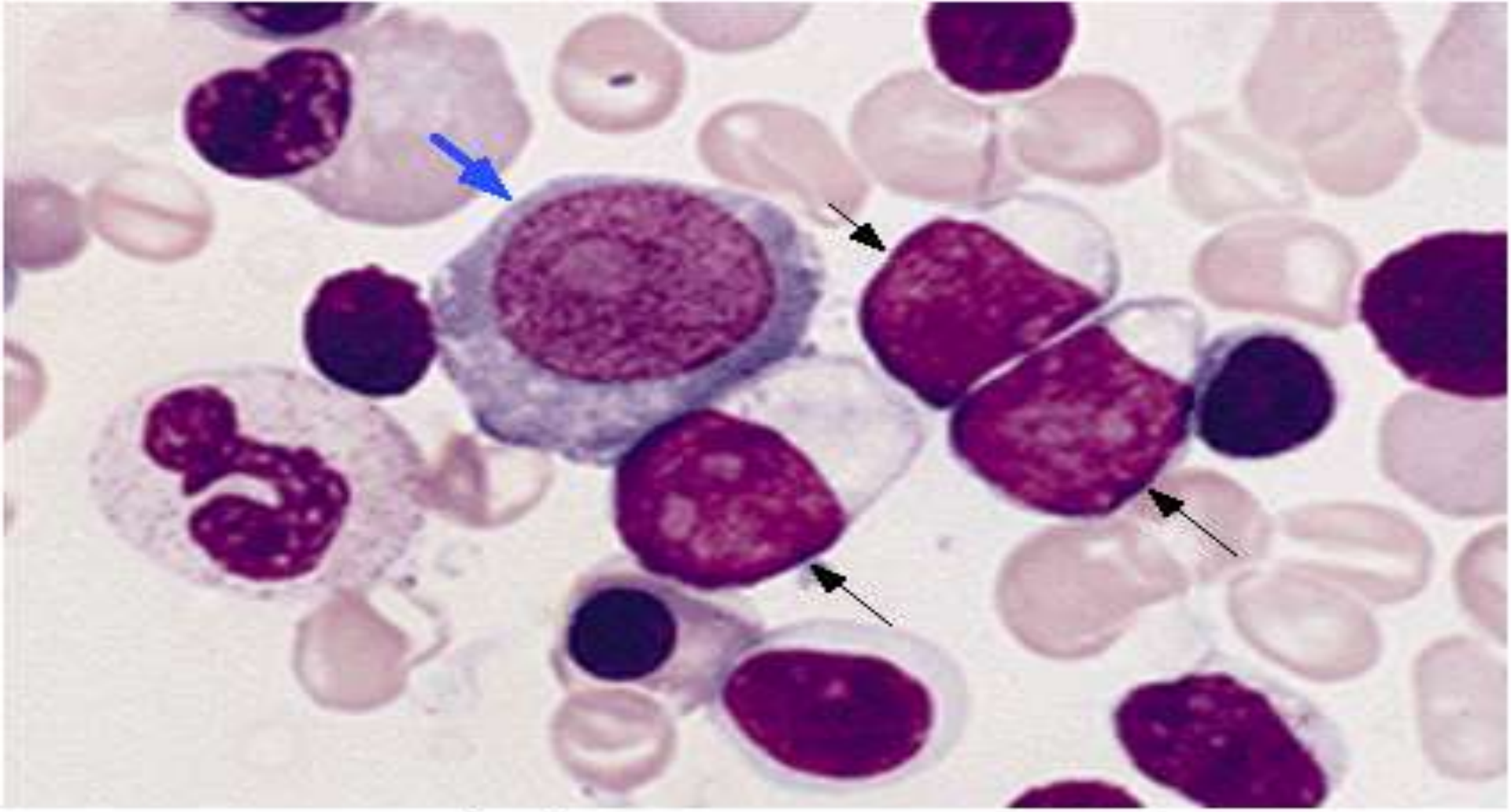
M3 "angel wings"- *Wright-Giemsa stain, 1000x*



Acute myelomonocytic leukemia (M4) Bone marrow smear from a patient with acute myelomonocytic leukemia (FAB classification M4). (Wright-Giemsa stain). The two promyelocytes on the left (black arrows) with basophilic cytoplasm containing coarse azurophilic granules contrast with the two promonocytes on the right (blue arrows) which have abundant pale cytoplasm and delicate nuclear folds. (From Brunning, RD, McKenna, RW. Tumors of the bone marrow. Atlas of tumor pathology (electronic fascicle), Third series, fascicle 9, 1994, Washington, DC. Armed Forces Institute of Pathology.)



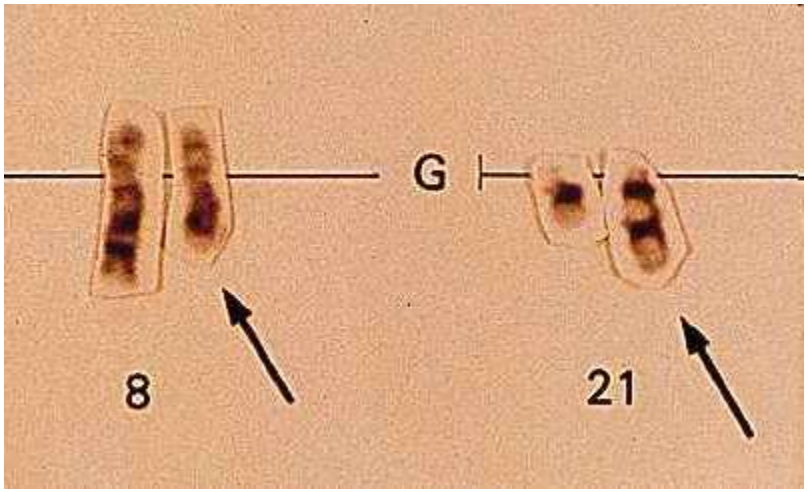
M4 Auer rods and hand-mirror appearing blasts
Wright-Giemsa, 1000x



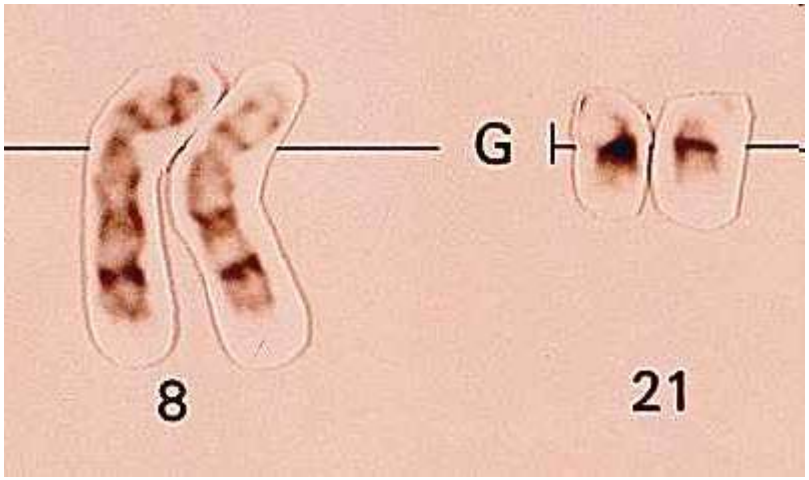
Erythroleukemia (M6) Bone marrow smear from a patient with erythroleukemia (FAB classification M6). (Wright-Giemsa stain). A megaloblastoid erythroblast (blue arrow) is shown along with three myeloblasts (black arrows). (From Brunning, RD, McKenna, RW. Tumors of the bone marrow. Atlas of tumor pathology (electronic fascicle), Third series, fascicle 9, 1994, Washington, DC. Armed Forces Institute of Pathology.)

Cytogenetics

- Since chromosomal abnormalities are associated with specific leukemia subtypes, response to therapy, and prognosis, cytogenetic analysis of bone marrow is an important component of the evaluation of a leukemic patient.
- Induction treatment may begin before cytogenetic results are available (using FAB classification), but decisions regarding consolidation are often based on cytogenetic risk groups.

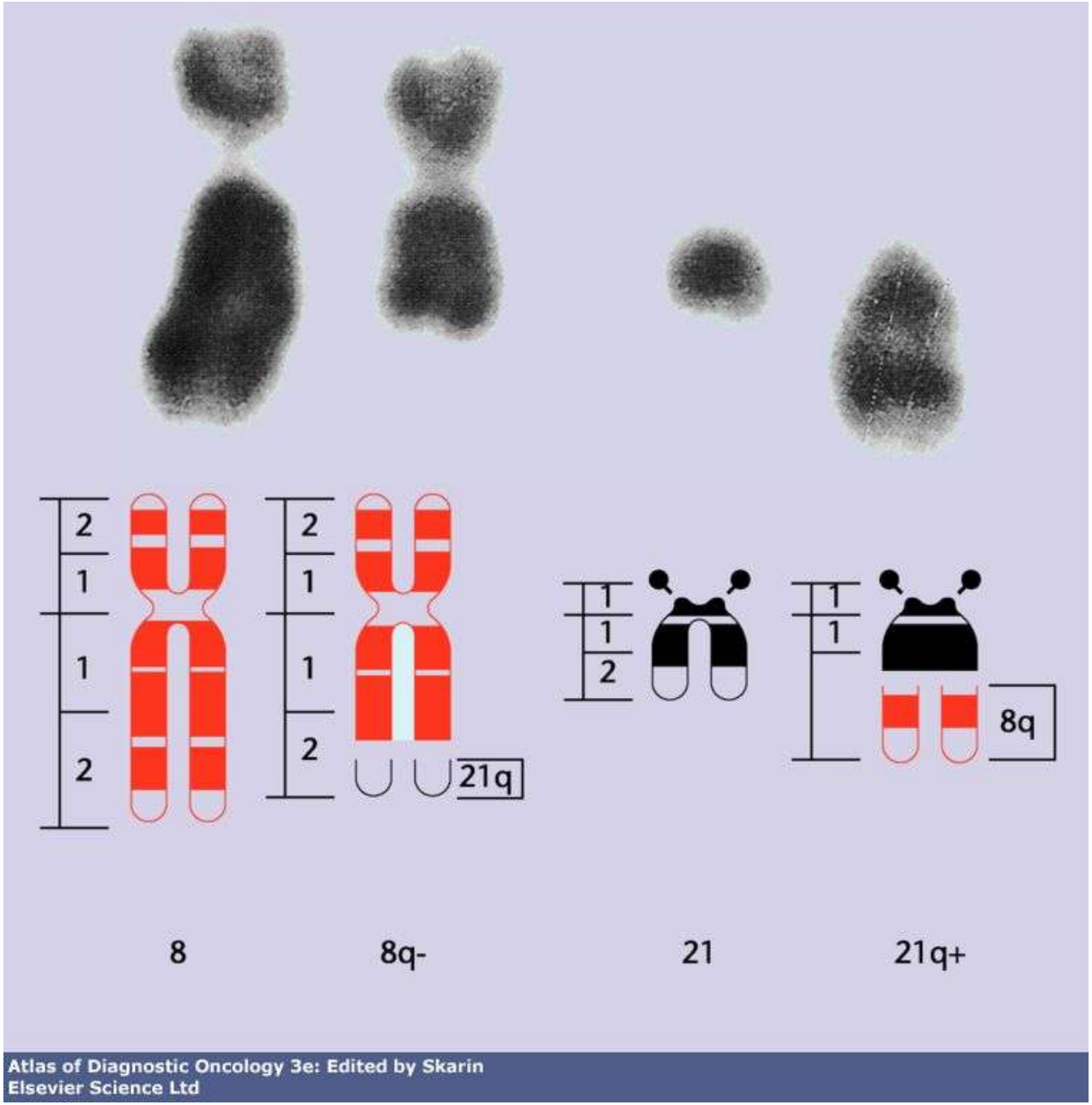


t(8;21) at diagnosis. The karyotype at diagnosis with a t(8;21) (arrows) as the only cytogenetic change. This translocation is usually seen in AML (M2) often associated with Auer rods, marrow eosinophilia, and a favorable prognosis.



Normal chromosomes during complete remission. All chromosomes appear normal. No karyotypes with t(8;21) were seen.

www.meds.com/leukemia/ guide/guide_chapter3.html



Atlas of Diagnostic Oncology 3e: Edited by Skarin
Elsevier Science Ltd

Immunophenotyping

- The immunophenotype of bone marrow cells is determined using monoclonal antibodies that recognize myeloid- and lymphoid-specific glycoprotein antigens (referred to as clusters of differentiation or CDs) on the surface of normal and leukemic hematopoietic cells.
- AMLs usually express the following Immunophenotypes:

✓ *All AML cells- CD13, CD15, CD33*

✓ *Monocytoid AML cells- CD14*

✓ *Blast cells (all lineages, particularly primitive cells)- CD34*

Table 7: Immunological characteristics in acute myeloid leukemia

Antigen	FAB classification						
	M0	M2 t(8;21)	M3 t(15;17)	M4Eo Inv16	M5	M5 t(9;11)	M7
MPO	+/-	+	+	+	-/+	-	-
CD2	-			+/-			
CD13	+/-	+	+	+	+/-	-	+/-
CD14	-	-	-	+/-	+/-	-	-
CD15	-	+/-	-/+	+/-		+	-
CD19	-	+/-					
CD33	+/-	+/-	+	+	+	+	+/-
CD34	+/-	+/-	-	-/+			
CD56		+/-					
CD61	-	-	-	-	-	-	+
CD64	-	-	+/-	+	+	+	
CDw65	-/+	+/-	-/+	+	+/-	+	+/-
CD117	+/-	+/-	-/+	+/-	-/+		
HLA-DR	+/-	+	-	+	+	+	+/-

-: Antigen not expressed, -/+: antigen expressed in less than 50 % of patients, +/-: antigen expressed in majority of patients, +: antigen expressed, open fields represent partial expression without specificity for diagnosis or lack of reliable data

www.classimed.de/eamocel2.html

Prognosis

- The median survival for untreated or refractory AML is usually a few weeks to 2-3 months.
- Patients who do not receive consolidation therapy will relapse, usually within 6 to 9 months.
- Despite the use of current induction and consolidation chemotherapy, most patients will eventually relapse and die of acute leukemia. Median survival is about 2 years (for patients < 60 years) and less for older patients.
- Approximately 25% to 40% of patients with AML treated with chemotherapy are alive and free of disease 5 years after diagnosis.

Acute lymphoblastic leukemia (ALL)

Definition

- Neoplastic disease which results from a mutation in a single lymphoid progenitor cell at one of several discrete stages of development B or T cells

Epidemiology

- Leukaemia is the most common malignancy in children and accounts for one-third of all childhood cancers.
- Approximately 3/4 of all cases of childhood leukaemia are ALL.
- About 3,000 children in the United States and 5,000 children in Europe are diagnosed with ALL each year.
- The peak incidence of ALL occurs between age 2 and 5 years. The incidence of ALL is higher among boys than girls.

French American British Classification

- L1: small uniform blasts
- L2: larger, more variable sized blasts
- L3: uniform cells with basophilic and sometimes vacuolated cytoplasm

Immunologic Subtype	% of cases	FAB Subtype	Cytogenetic Abnormalities
Pre-B ALL	75	L1, L2	t(9;22), t(4;11), t(1;19)
T cell ALL	20	L1, L2	14q11 or 7q34
B cell ALL	5	L3	t(8;14), t(8;22), t(2;8)

From: Harrison's Principles of Internal Medicine, 16th ed. 2005. Chapter 97, Malignancies of lymphoid cells.

WHO Classification

- **Precursor lymphoid neoplasms**
- *B lymphoblastic leukaemia/lymphoma*
- B lymphoblastic leukaemia/lymphoma, NOS
- B lymphoblastic leukaemia/lymphoma with recurrent genetic abnormalities
- B lymphoblastic leukaemia/lymphoma with t(9;22)(q34; q11.2); *BCR-ABL1*
- B lymphoblastic leukaemia/lymphoma with t(v;11q23); *MLL rearranged*
- B lymphoblastic leukaemia/lymphoma with t(12;21)(p13; q22); *TEL-AML1 (ETV6-RUNX1)*
- B lymphoblastic leukaemia/lymphoma with Hyperdiploidy
- B lymphoblastic leukaemia/lymphoma with hypodiploidy (hypodiploid ALL)
- ***T lymphoblastic leukaemia/lymphoma***

Table 2. Acute lymphoblastic leukemia (ALL): incidence & biological differences.

	Children	Adults
Peak incidence	5 years	50 years
% of Leukemias	80-85%	15%
Chromosomes		
Ph^+	3%	30%
MLL	1-2%	7%
TEL/AML1	20%	2%
Hyperdiploid	25%	5%
T-cell	10-15%	20-25%
Mature B	1-2%	3-5%

http://asheducationbook.hematologylibrary.org/content/2006/1/128.full.pdf

Pathogenesis

- Acquired Genetic Change in Chromosome
  - Change in number, ie ploidy
  - Change in structure
    - Translocations (most common)
    - Inversions
    - Deletions
    - Point mutations
    - Amplifications

      Changes in normal means of cell differentiation, proliferation, and survival

Symptoms

- The first symptoms are usually non-specific and include anorexia, irritability and lethargy.
- Fever is the most common finding, occurring in approximately 60% of patients.
- Progressive bone marrow failure leads to pallor (anemia), bleeding (thrombocytopenia) and susceptibility to infections (neutropenia). Over one third of patients may present with a limp, bone pain, arthralgia or refusal to walk due to leukaemia infiltration of the periosteum, bone or joint, or to the expansion of the marrow cavity by leukaemia cells.
- Less common signs and symptoms include headache, vomiting, respiratory distress, oliguria and anuria.
- At initial diagnosis, 60 to 70% of children have enlargement of the liver or spleen, usually asymptomatic.
- Lymphadenopathy (usually painless, localized or generalized) due to leukaemia infiltration is an frequent presenting sign.

CNS symptoms

- Acute leukemia, in particular ALL, has the highest propensity to invade the meninges and result in leukemic meningitis (LM)

– Headache (<5% cases)

– Increased ICP

- Vomiting
- Lethargy
- Papilledema

– Cranial nerve abnormalities

Physical Examination

- **Clinical and laboratory features at diagnosis in children with ALL**

Clinical and laboratory features	Percentage of patients
Symptoms and physical findings	
Fever	60
Hepatosplenomegaly	70
Paleness	55
Bleeding (e.g., petechiae or purpura)	50
Lymphadenopathy	50
Bone pain	25
Abdominal pain	20
Weight loss	15

https://www.orpha.net/data/patho/Pro/en/AcuteLymphoblasticLeukemia-FRenPro3732.pdf

Leukemic infiltration of the meninges

19 year old female with ALL

Axial contrast enhanced T1-weighted MR image demonstrates multiple enhancing subarachnoid nodules (arrows) consistent with leukemic meningitis.

Peripheral Blood Findings

Clinical and laboratory features	Percentage of patients
Laboratory features	
Leukocyte count (mm^3)	
<10,000	53
10,000–49,000	30
>50,000	17
Hemoglobin (g/dL)	
< 7.0	43
7.0 - 11.0	45
> 11.0	12
Platelet count (mm^3)	
< 20.000	28
20.000 – 99.000	47
> 100.000	25

Cytochemistry

- Terminal deoxynucleotidyl transferase (Tdt): DNA polymerase in early lymphoblasts
- PERIODIC ACID-SCHIFF (PAS)
  - *Principle:*
  - *Periodic acid oxidizes glycogen, mucoproteins band other high molecular weight carbohydrate into ALDEHYDE*
  - *Aldehyde + colorless schiff reagent ---bright red pink*

Periodic Acid Schiff

-Red deposit

Immunophenotyping ALL

Table 4 Panel of antibodies for the diagnosis of acute leukaemias

	B-lymphoid	T-lymphoid
First line:	CD79a*, CD22* CD19, CD10	CD3*, CD2
Second line:	SmIg (kappa/lambda) CytIg, CD138	CD7

Cytogenetic Abnormalities

TABLE 2. Cytogenetic-Molecular Abnormalities in ALL*[69-78]

Category	Genes	Cytogenetics	Frequency (%)	
			Adult	Children
Hyperdiploid			2-15	10-26
Hypodiploid			3-10	3-10
Pseudodiploid	*BCR-ABL*	t(9;22)(q34;q11)	15-25	2-6
	p16, p15	del(9)(p21-22)	6-30	20
	MLL	t(4;11),t(9;11), t(11;19),t(3;11)	5-10	<5
	ATM	del(11)(q22-23)	25-30†	15†
	TEL-AML-1	t(12;21)(p12;q22)	<1‡	20-25‡
	E2A-PBX1, E2A-HLF	t(1;19),t(17;19)	<5	<5
	TAL-1	t(1;14)(p32;q11)	10-15	5-10
	TAL-2	t(7;9)(q34;q32)	<1	<1
	HOX11	t(10;14)(q24;q11)	5-10	<5
	HOX11L2	t(5;14)(q35;q32)	1	2-3
	TCR	t(1;14)(p32;q11)	20-25§	20-25§
	miR15/miR16	del(13)(q14)	<5	<5
	c-myc	t(8;14),t(8;22),t(2;8)	5	2-5
	NR	+8	10-12	2
	NR	del(7p)	5-10	<5
	NR	del(5q)	<2	<2
	NR	del(6q),t(6;12)	5	<5

*ALL = acute lymphoblastic leukemia; NR = not reported.
†Determined by loss of heterozygosity.
‡Determined by polymerase chain reaction.
§In T-cell ALL, overall incidence <10%.

From: Jabbour, E. et al. Adult Acute Lymphoblastic Leukemia. *Mayo Clinic Proc.* 2005;80(11):1517-1527

Prognosis

- Overall better in children than in adults

Table 2
Clinical and biologic factors predicting clinical outcome

Factor	Favorable	Unfavorable
Age at diagnosis	1–9 years	<1 or >9 years
Sex	Female	Male
White blood cell count	Low (eg, <50 or <25 × 10^e9/L)	High (eg, >50 or >25 × 10^e9/L)
Genotype	Hyperdiploidy (>50 chromosomes) t(12;21) or *TEL/AML1* fusion	Hypodiploidy (<45 chromosomes) t(9;22) or *BCR/ABL* fusion t(4;11) or *MLL/AF4* fusion
Immunophenotype	Common, preB	ProB, T-lineage

http://pediatrics.evms.edu/residency/resgoals/hemeonc/hemeoncresallreview.pdf

Prognosis

Table 3. Five-year event-free survival.

	Children	Adults
Pre-B	> 80%	30-40%
T-cell	75-80%	45-55%
Ph^+	20-25%	< 10%
MLL	40-50%	20%
TEL/AML1	90%	N/A

Treatment of acute leukemias

Goal of treatment

- The goals of therapy are to eliminate the leukemic clone and to restore normal hematopoiesis.
- A complete remission (CR) is defined as the presence of less than 5% blasts in the bone marrow and restoration of normal blood counts.
- The length of patient survival correlates with achieving a CR and the duration of the CR.
- Patients who have refractory disease or do not achieve CR (often with more than one attempt at induction therapy) usually die within 2 to 4 months of diagnosis, due to complications such as infection or bleeding.

Treatment regimens

- **Induction therapy** – is intended to induce a complete remission via the elimination or significant reduction of tumor clone and normalization of hematopoesis
- **Consolidation of therapy -** the goal of consolidation therapy is to eliminate residual leukemic cells, prevent relapse, and improve survival.
- **Maintenance treatment**
- **Treatment of relapses -** once the leukemia relapses, patient outcome is poor.
- **Therapy for refractory disease**
- **Prevention of neuroleukemia**

Treatment strategies

- Chemotherapy
- Molecularly targeted therapy
- Radiation therapy
- *Prevention neuroleukemia*
- *Reduction of splenomegaly*
- *Radiation of painful bone sites*
- *Preparation before a bone marrow transplantation*
- Allogeneic Stem Cell Transplantation or Autologous Bone Marrow Transplantation

The end