Academic Activity
AML
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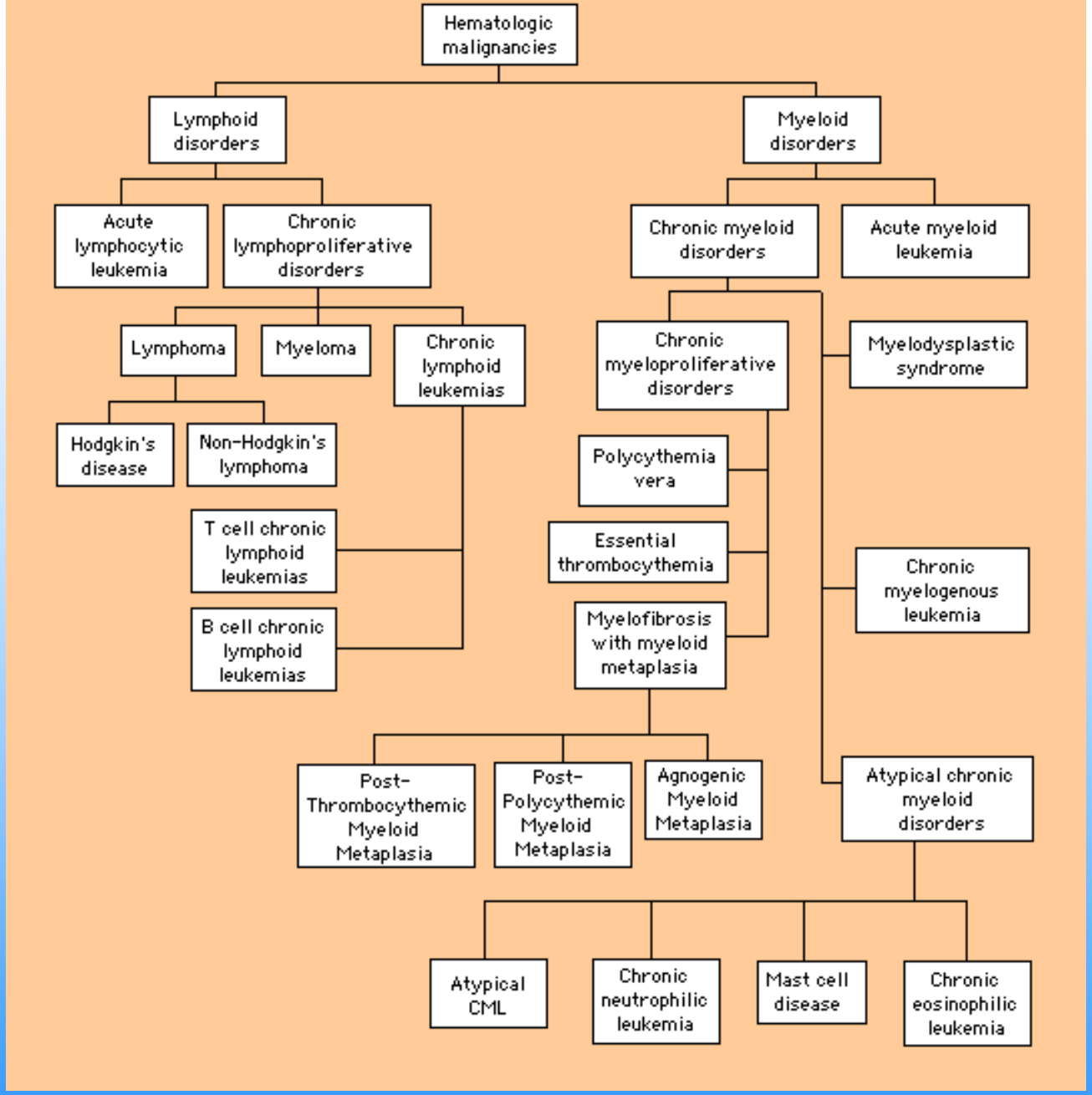
Objectives:

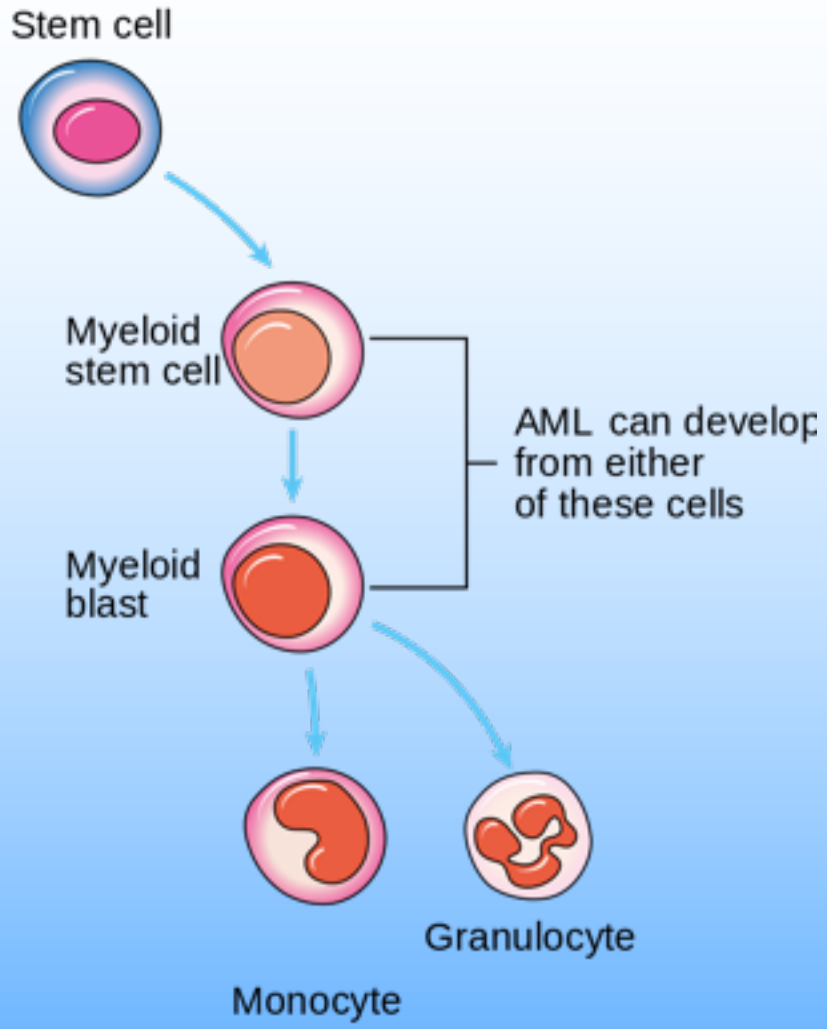
- Define diagnosis, incidence, etiology, and classification of acute myeloid leukemia
- Describe clinical presentation and complications of disease
- Review diagnostic workup and prognostic factors
- Outline treatment modalities available, as well as impact of age, relapse, and refractory disease

Papers for AML

- Cytogenetic & AML outcome: MRC
- Genomic clasification & prognosis
- ELN 2-17 guidelines
- RATIFY study
- AML elderly guidelines
- AZA-AML-001
- APL guidelines
- Lo-Coco APL study

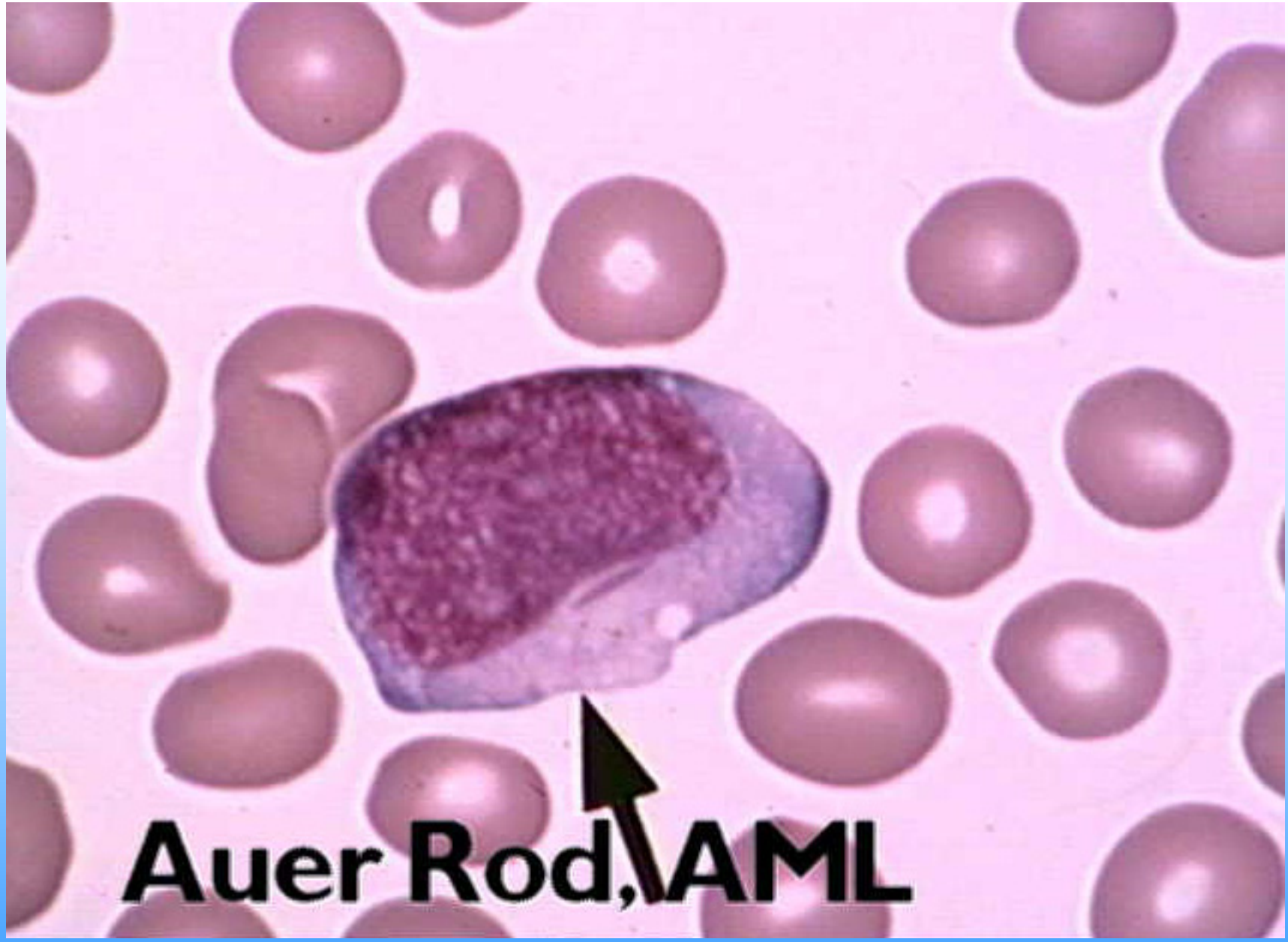
Conceptual Organization of Hematologic Malignancies




Stem cell
Myeloid stem cell
AML can develop from either of these cells
Myeloid blast
Granulocyte
Monocyte

Acute Myeloid Leukemia: Diagnostic Criteria

- Diagnosis depends on morphologic identification of leukemic myeloblasts in peripheral blood and bone marrow
- Leukemic myeloblasts characterized by
  - Larger cells with round-to-irregular nuclei, distinct nucleoli, little cytoplasm, and fine azurophilic granules
  - Auer rods (azurophilic granules within lysosomes)
  - Myeloblasts characterized by aberrant or arrested maturation


Auer Rod, AML

Acute Myeloid Leukemia:

- Represents heterogeneous group of diseases characterized by infiltration of bone marrow, blood, and other tissues by clonal neoplastic cells of hematopoietic system (myeloblasts)
- Presence of over 20% leukemic blasts in bone marrow aspirate required for definitive diagnosis

Acute Myeloid Leukemia:

- Acquired genetic changes in stem cells cause block in maturation, and lead to
  - Activation of growth-promoting proto-oncogenes
  - Inactivation of tumor suppressor genes
  - Alterations in transcription factors
- Chromosomal translocation generates fusion proteins that disrupt normal transcription factors critical for myeloid differentiation

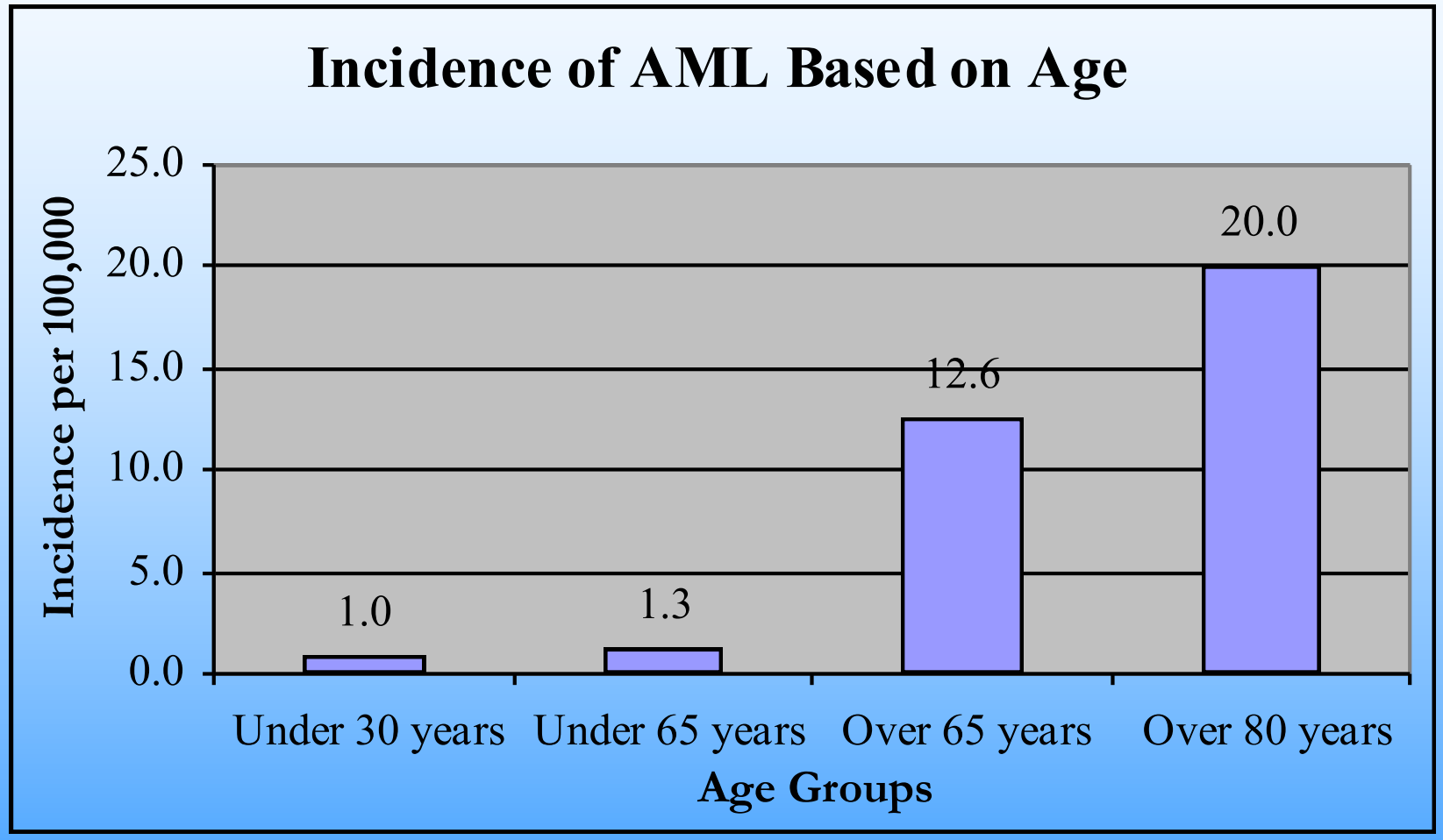
Acute Myeloid Leukemia:

- Unlike normal hematopoiesis, clonogenic leukemia cells generally retain limited ability to differentiate into different lineages
- Abnormalities in apoptosis promote persistence of leukemic clone
- Abnormalities in telomerase promote longevity
- Leukemogenic translocation or mutations result in dysregulation of cell cycle

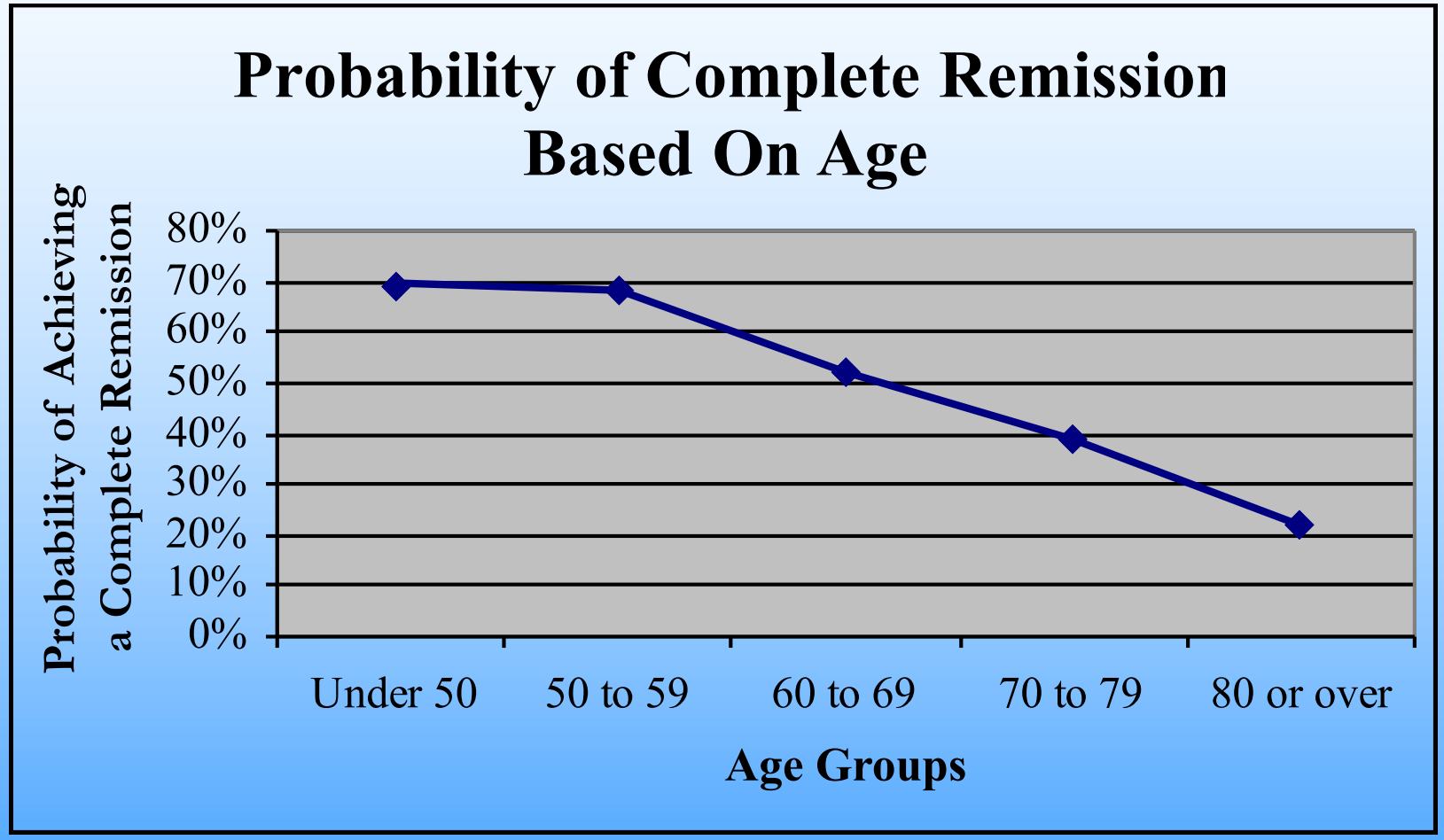
Acute Myeloid Leukemia: Incidence

- Represents most common variant of acute leukemia in adults
- Accounts for 80 to 85% of acute leukemia in individuals over twenty years of age
- Age-adjusted incidence higher in males than in females
- Median age of sixty-five years
- Overall incidence of 2.3 per 100,000 per year
- Incidence increases progressively with age

Acute Myeloid Leukemia: Incidence



Relationship Between Age and Complete Remission:



Acute Myeloid Leukemia: Etiology

- Cellular transformation represents multi-step process
- Excessive chromatin fragility
  - Fanconi's anemia and Bloom's syndrome
  - Ataxia telangiectasia
- Cigarette smoking, benzene, ethylene oxide, herbicides, and pesticides

Acute Myeloid Leukemia: Etiology

- Previous hematologic disorders
  - Severe congenital neutropenia
  - Myeloproliferative disorders
  - Myelodysplastic syndrome (20% progresses to AML)
  - PNH
- Previous exposure to radiation or leukemogenic agents
  - Often component of therapy for unrelated neoplasm
  - Radiation (increased incidence peaks five to seven years after exposure)
  - Drugs

Drug-Induced AML:

- Expected to develop in 3 to 10% of patients treated with **alkylating agents**
  - Risk peaks five to ten years after start of chemotherapy ("long latency period")
  - Frequently preceded by myelodysplasia
  - Associated with deletions of chromosomes 5 and 7, and complex chromosomal abnormalities

Drug-Induced AML:

- Also represents complication of treatment with **topoisomerase II inhibitors**
  - Epidophyllotoxins and anthracyclines
  - Risk peaks two to three years after start of chemotherapy ("short latency period")
  - Not preceded by myelodysplasia
  - Frequently associated with 11q23 chromosomal abnormalities (associated with monocytic disease)
  - Risk proportional to dose intensity (not cumulative dose)

Classification of AML:

- Categorized into biologically distinct groups based on cell morphology, cytochemistry, and immunophenotype as well as cytogenetic and molecular analysis
- Flow cytometry identifies cells by surface antigens (cluster differentiation designation)
- Chromosomal classification provides most important pre-treatment prognostic information

FAB Classification of AML:

M_0	AML with minimal differentiation	5%
M_1	AML without maturation	15%
M_2	AML with maturation	25%
M_3	Acute promyelocytic leukemia	10%
M_4	Acute myelomonocytic leukemia	25%
M_5	Acute monocytic leukemia	5%
M_6	Acute erythroleukemia	5%
M_7	Acute megakaryocytic leukemia	10%

WHO 2016 Classification of AML

(Blood 2016;127:2391)

Acute myeloid leukemia (AML) and related neoplasms
AML with recurrent genetic abnormalities
AML with t(8;21)(q22;q22.1);*RUNX1-RUNX1T1*
AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22);*CBFB-MYH11*
APL with *PML-RARA*
AML with t(9;11)(p21.3;q23.3);*MLLT3-KMT2A*
AML with t(6;9)(p23;q34.1);*DEK-NUP214*
AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2*, *MECOM*
AML (megakaryoblastic) with t(1;22)(p13.3;q13.3);*RBM15-MKL1*
Provisional entity: AML with BCR-ABL1
AML with mutated *NPM1*
AML with biallelic mutations of *CEBPA*
Provisional entity: AML with mutated RUNX1
AML with myelodysplasia-related changes
Therapy-related myeloid neoplasms
AML, NOS
AML with minimal differentiation
AML without maturation
AML with maturation
Acute myelomonocytic leukemia
Acute monoblastic/monocytic leukemia
Pure erythroid leukemia
Acute megakaryoblastic leukemia
Acute basophilic leukemia
Acute panmyelosis with myelofibrosis
Myeloid sarcoma
Myeloid proliferations related to Down syndrome
Transient abnormal myelopoiesis (TAM)
Myeloid leukemia associated with Down syndrome

AML M_2 (with Maturation):

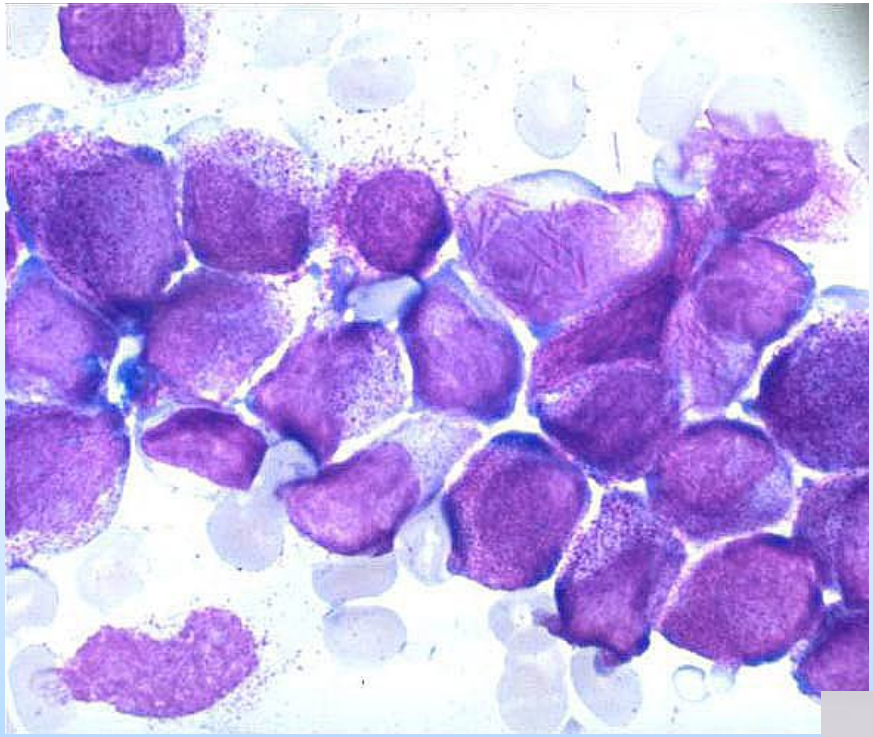
- Median age of thirty years
- High initial response to chemotherapy (85%)
- Good long-term disease-free survival
- Low relapse rate
- t(8;21) occurs in 40% of patients with AML M_2
  - Confers sensitivity to cytarabine
  - Persistence of fusion gene transcript in bone marrow samples fails to impact upon long-term remission

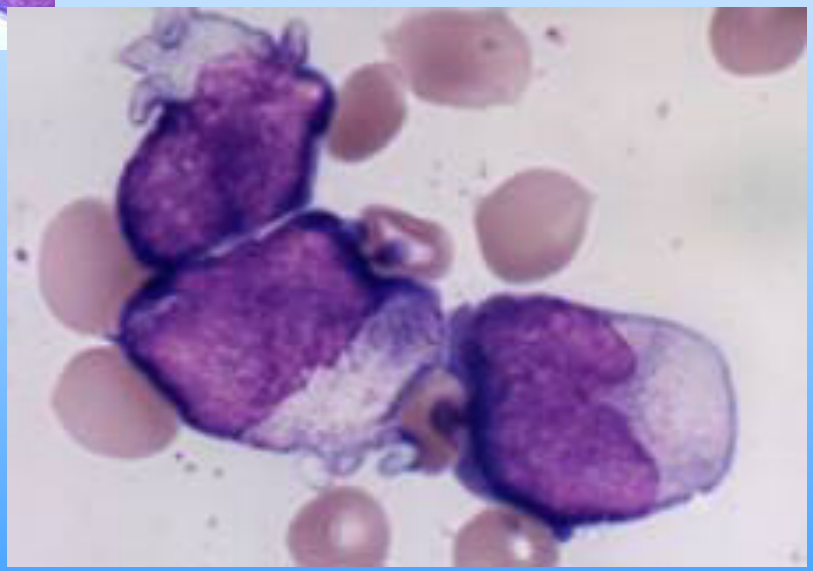
AML M_3: Acute Promyelocytic Leukemia

- Bone marrow demonstrates replacement by heavily granulated blasts with round nuclei, obvious nucleoli, and large azurophilic granules
- t(15;17) occurs in 98% of patients with AML M_3
  - Persistence of fusion gene transcript (detected by RT-PCR) heralds relapse within six months
  - Relapse occurs in small subset with negative RT-PCR
- Inherently low levels of *P*-glycoprotein confer sensitivity to **anthracyclines** and good prognosis

Cytogenetics: t(15;17) of AML M_3 after ATRA

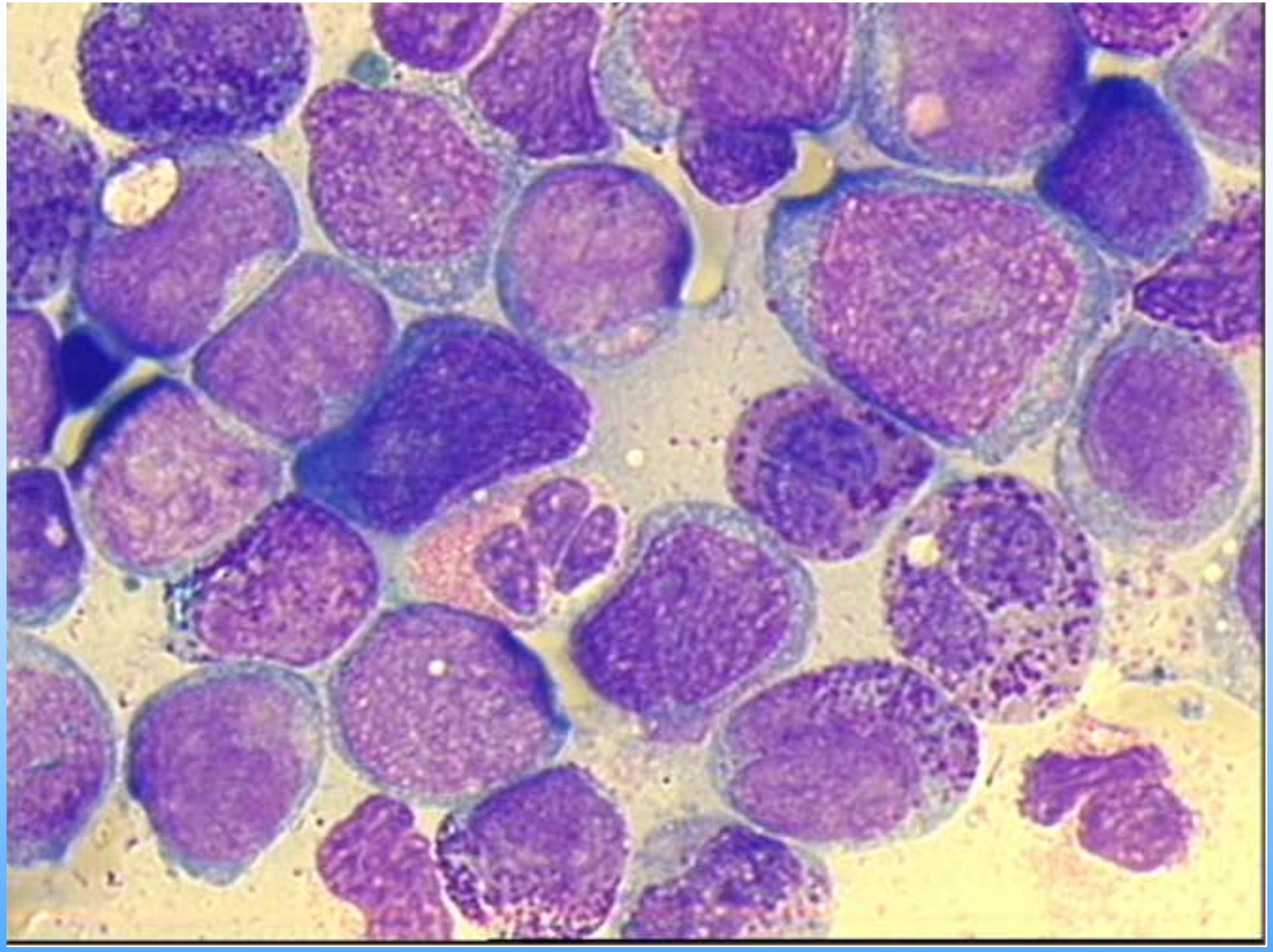
- Post-treatment marrow examinations frequently remain cellular with abnormal progranulocytes
- Subsequent marrow examinations demonstrated disappearance of progranulocytes with return of normal hematopoiesis
- Stable or improvement in blood counts with return of erythroid and megakaryocytic precursors confirm further chemotherapy not required





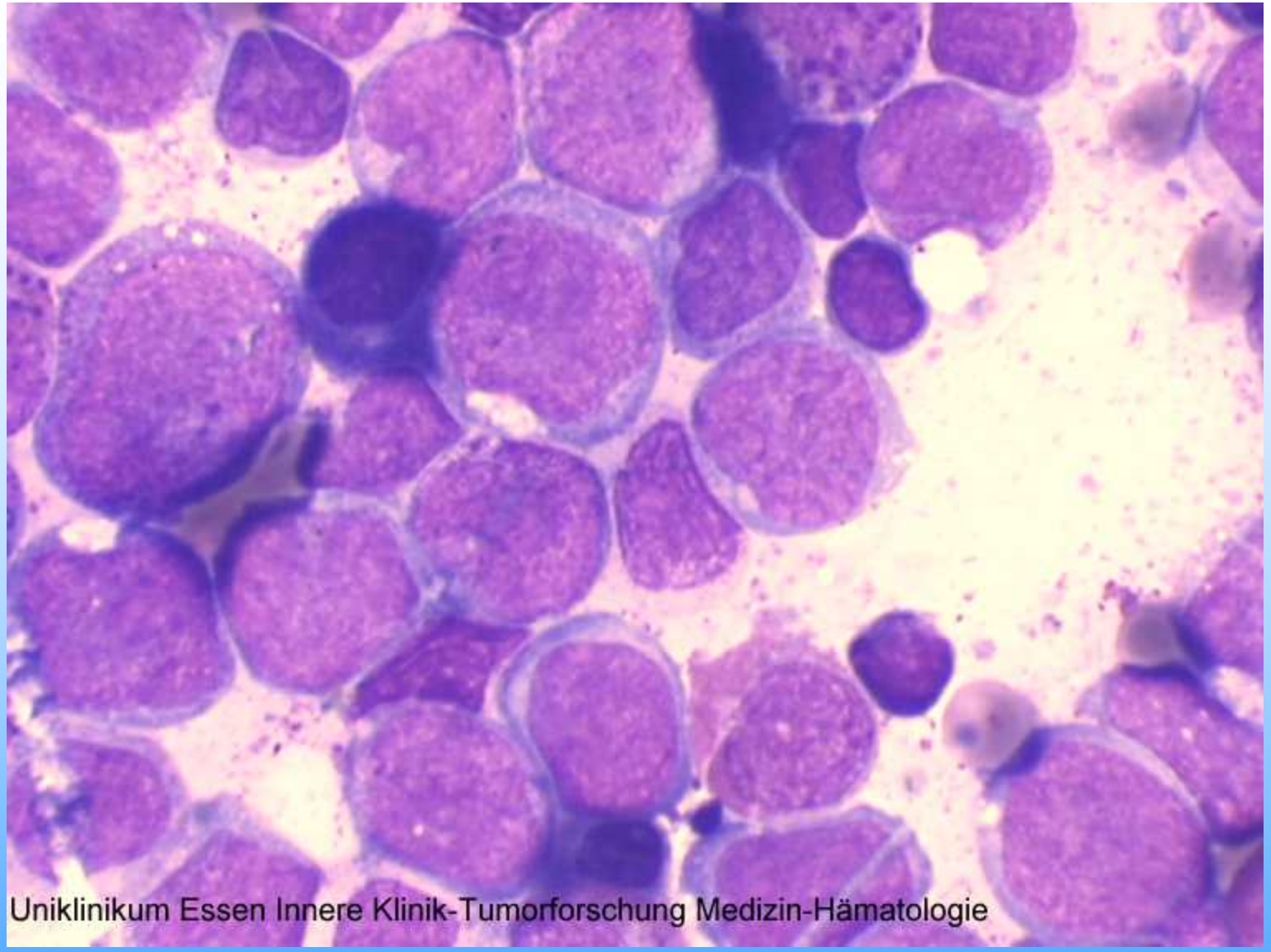
AML $M_{4\ Eo}$: AML with Eosinophilia

- Young age
- Hyperleukocytosis
- Extramedullary involvement
- Excellent prognosis (complete remission rates over 85%)
- Associated with inv(16)
- 60% three-year disease-free survival after high-dose cytarabine



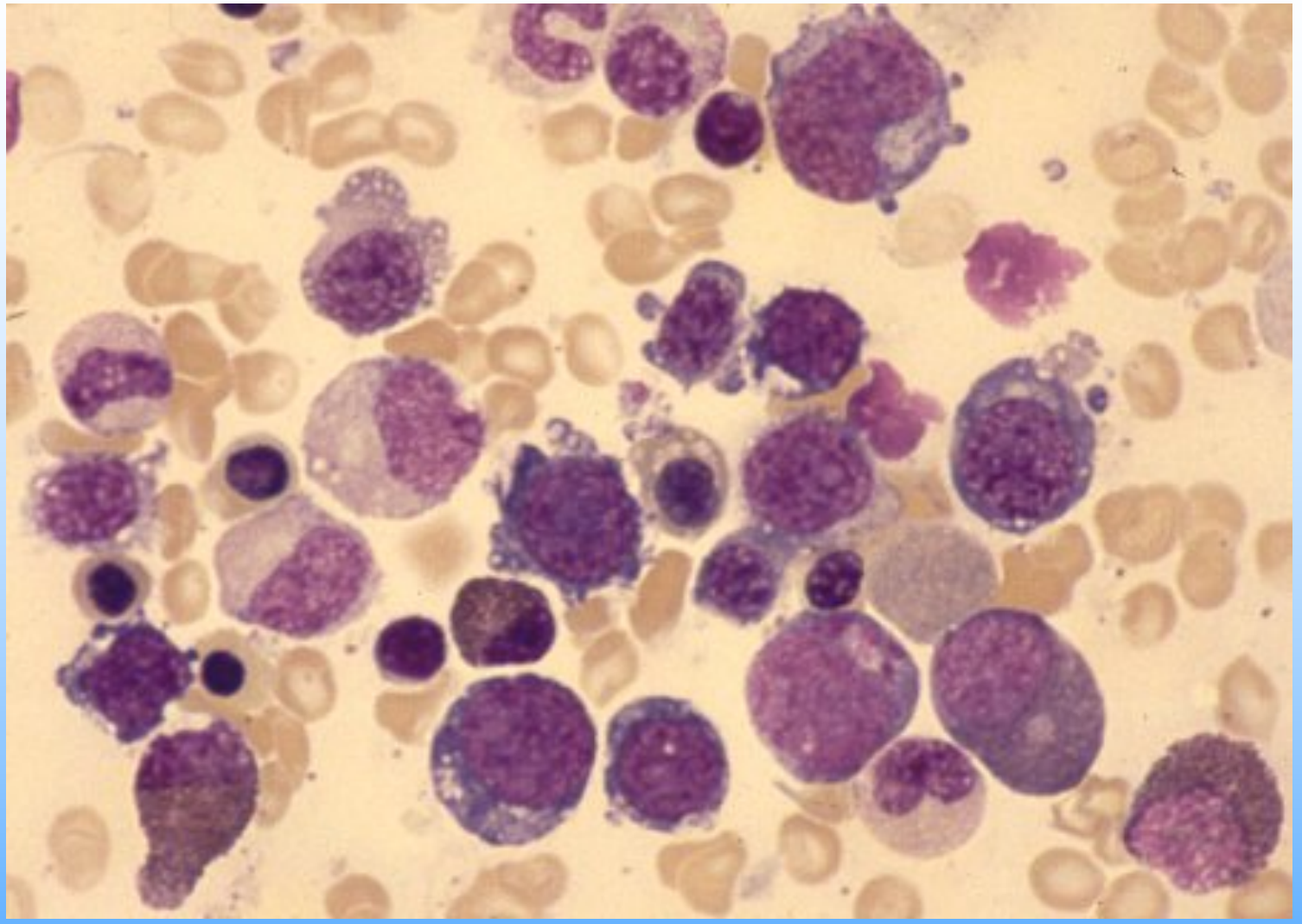
AML M_5: Acute Monocytic Leukemia

- High blast counts at diagnosis
- Serum lysozyme affects renal tubular function
  - Predisposes to severe symptomatic hypokalemia (exacerbated by antibiotics, amphoteracin B, emesis, and/or diarrhea)
  - Generally resolves with cytoreduction
- Highest incidence of extramedullary leukemia
- Associated with lower response rates (*cf.* initial drug resistance), shorter duration, and inferior long-term disease-free survival


Uniklinikum Essen Innere Klinik-Tumorforschung Medizin-Hämatologie

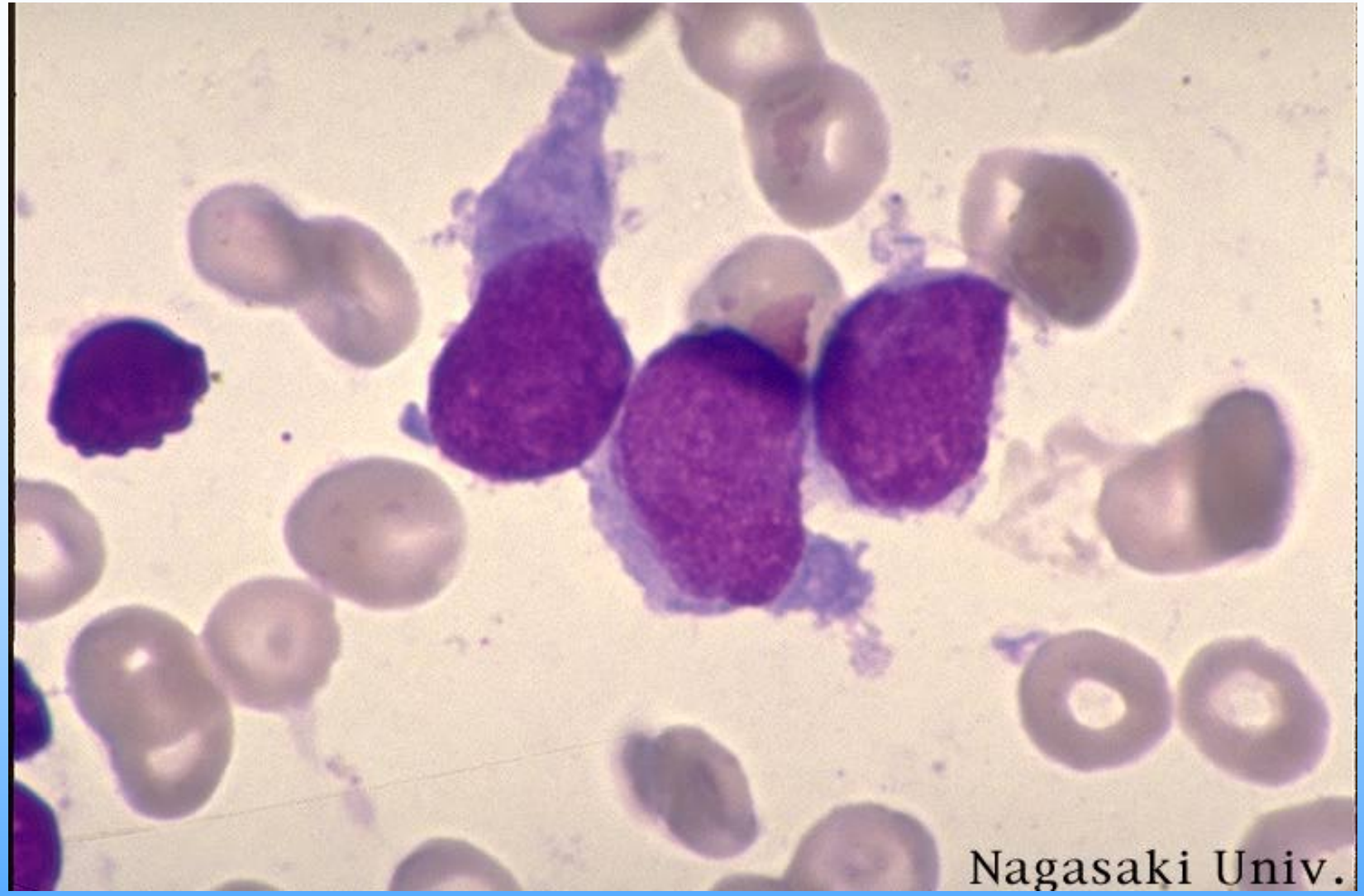
AML M_6: Acute Erythroleukemia

- Characterized by marked dysplastic changes in all three hematopoietic lines with eventual increase in blast count (*cf.* myelodysplasia)
- Older age groups
- Complex karyotypic abnormalities
- Demonstrates very poor response to therapy



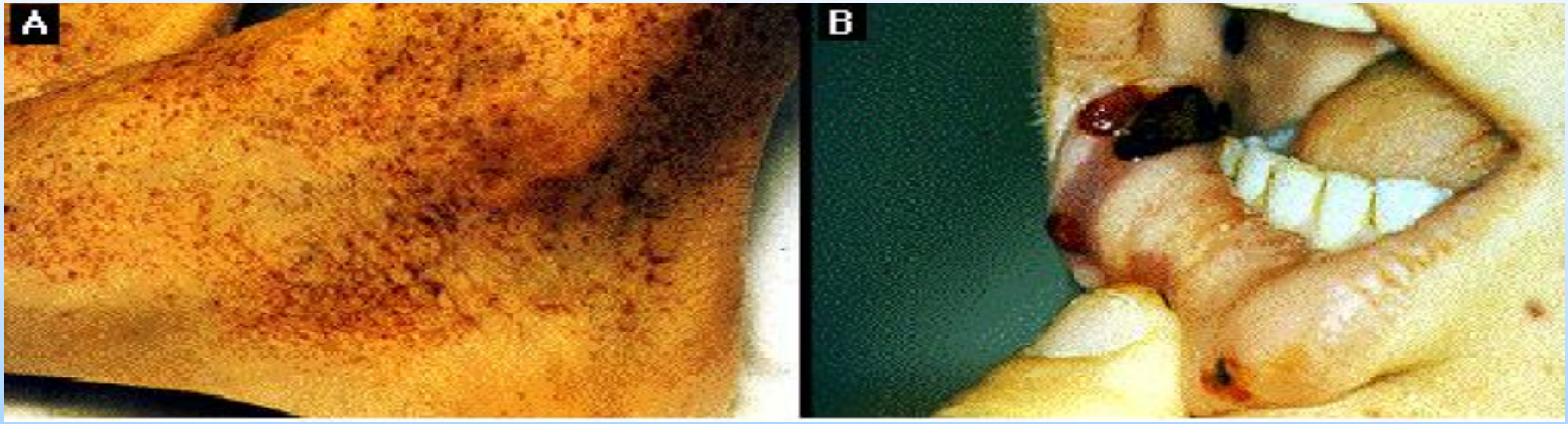
AML M_7: Acute Megakaryocytic Leukemia

- Associated with increased marrow fibrosis
- Poor response to initial therapy
- Poor overall survival

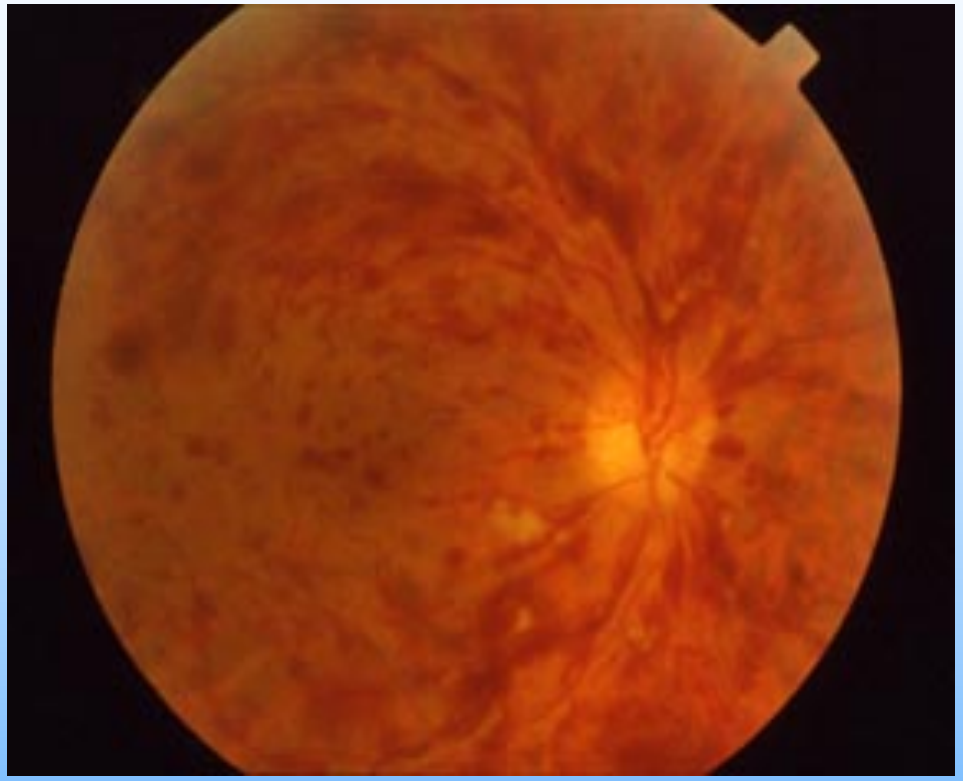

Nagasaki Univ.

Clinical Presentation:

- Diverse and non-specific symptoms often related to complications of pancytopenia (e.g.: fever, infection, pallor, hemorrhage, fatigue, exertional dyspnea)
- Palpable lymphadenopathy, hepatomegaly, or splenomegaly suggests ALL or CML blast crisis
- Neurologic symptoms rare (e.g.: headache, nausea, emesis, cranial neuropathies)

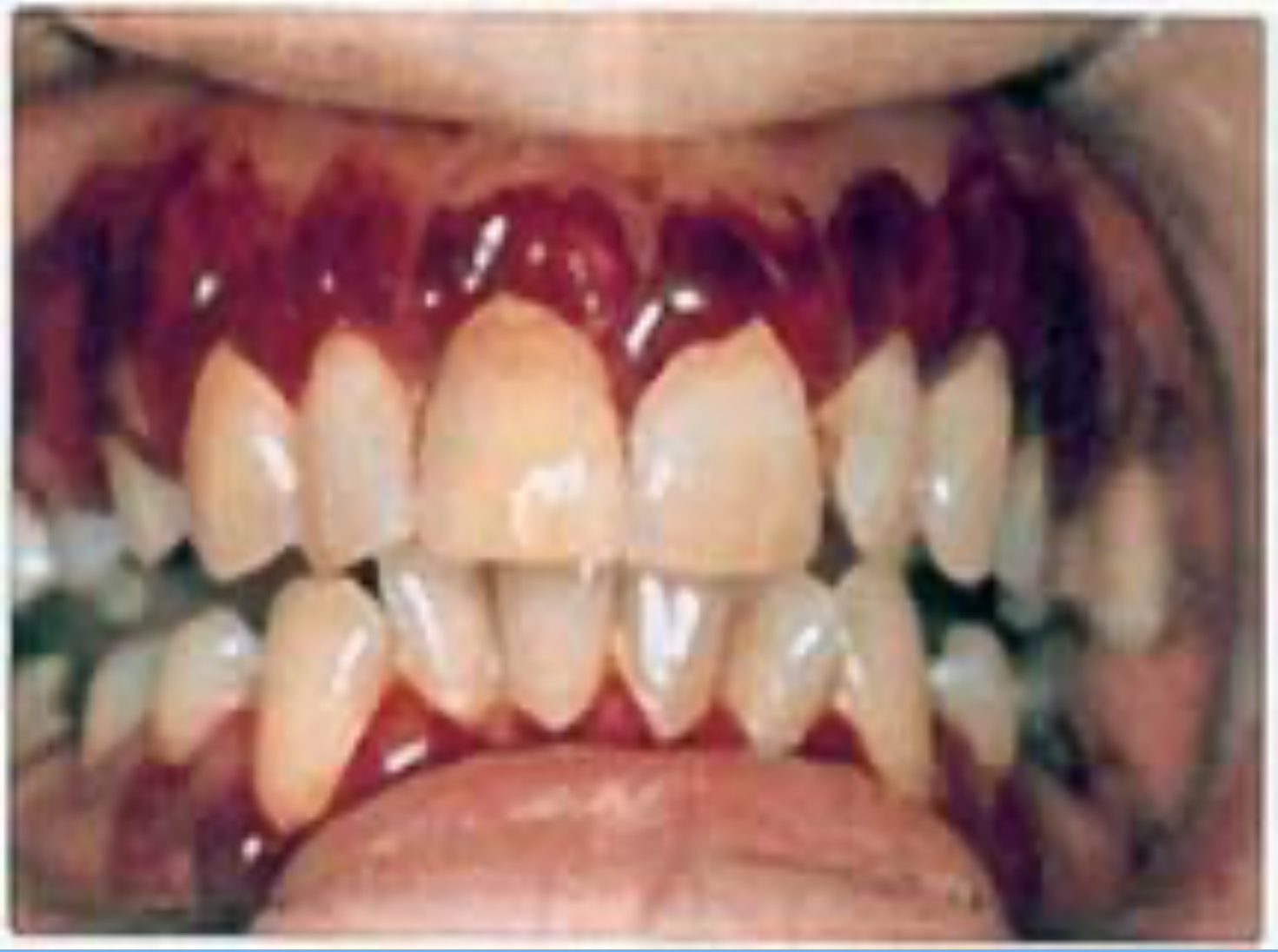

A
B

AML



Clinical Presentation:

- Infiltration of gingivae, skin, soft tissues, or meninges with leukemic blasts characteristic of monocytic subtypes (M_4 and M_5)
- Granulocytic sarcoma ("chloroma")
  - Represents isolated mass of leukemic blasts
  - Common in AML-M_2 with t(8;21)
  - Occurs in soft tissues, lung, mediastinum, breast, uterus, ovary, cranial or spinal dura, prostate, gastrointestinal tract, or bone
- Metabolic abnormalities



Complications of AML: Hyperleukocytosis

- Myeloblasts considerably less deformable than mature myeloid cells and considerably more "sticky" than lymphoblasts due to expression of cell surface adhesion molecules
- Myeloblast counts over 100 x 10^9/L
  - Represent **medical emergency**
  - Impede blood flow in microcirculation and predispose to local hypoxia ("leukostasis")
  - Exacerbated by high metabolic activity of blasts

Complications of AML: Hyperleukocytosis

- Leukostasis signaled by CNS and/or pulmonary symptoms (e.g.: ocular and cerebrovascular dysfunction, dyspnea)
- More common in patients with myelomonocytic or monocytic leukemias
- Associated with lower remission rates and shorter duration of remission due to larger initial tumor mass, as well as biologic and intrinsic chemoresistance

Complications of AML: Hyperleukocytosis

- Rapid cytoreduction achieved with chemotherapy (*cf.* tumor lysis syndrome)
  - Standard induction agents
  - High-dose hydroxyurea
- Leukapheresis indicated if initiation of chemotherapy not immediately available
  - Renal insufficiency
  - Delays in initiation of allopurinol
  - Metabolic problems

Complications of AML: CNS Disease

- Occurs in less than 5% of AML
- Diagnostic lumbar puncture not routinely indicated in AML in absence of symptoms
  - Cytarabine penetrates into CNS
  - All-*trans*-retinoic acid fails to penetrate into CNS
- Reactive ependymal cells resemble leukemia cells after administration of intrathecal chemotherapy

Complications of AML: CNS Disease

- Methotrexate 12 mg or cytarabine 50 mg used as initial therapy with cross-over to other agent in event of refractory disease or relapse
- Typical schedule administers treatment two or three times weekly until cerebrospinal fluid clear, two subsequent doses on weekly schedule, then monthly administration for balance of year
- Omaya reservoir permits intraventricular drug administration

Complications of AML: CNS Disease

- Associated with high rate of relapse rate, even after initially successful therapy
- Incidence increased with hyperleukocytosis as well as $M_{4\ Eo}$ and M_5
- Leukemias may infiltrate every ocular structure (most commonly involve choroid and retina)
- Characterized by retinal hemorrhage and cotton wool spots (nerve fiber ischemia)

Complications of AML: Metabolic Abnormalities

- Hyperuricemia
  - Predisposes to urate nephropathy and renal insufficiency
  - Ameliorated with allopurinol, hydration, and alkalinization
  - High risk Use of rasburicase advocated
- Tumor lysis syndrome related to massive leukemic cell death
  - Characterized by hyperphosphatemia, hypocalcemia, hyperkalemia, and renal insufficiency

Diagnostic Workup:

- History and physical examination
  - Duration of symptoms
  - Menstrual history and prior pregnancies
  - Prior transfusions, or history of transfusion reactions
  - Drug allergies, especially to antibiotics
  - Signs and sites of infection
  - Signs of extramedullary leukemia
  - Dentition status

Diagnostic Workup:

- Blood counts, chemistries, and coagulation profile
- Bone marrow aspirate and biopsy (provides morphology, cytochemistry, immunophenotype, cytogenetics, and molecular studies)
- Chest x-ray
- Electrocardiogram, MUGA or ECHO
- Lumbar puncture, if symptomatic
- Blood type and HLA determination
- Viral serology (HIV, Hepatitis, CMV &HSV)

Initial diagnostic approach: Induction candidates

Bone marrow aspirate for:

- Morphology
- Flow cytometry: MPFC
- Cytogenetics
- Mutational profiling
  - Rapid PCR (within 7 days):
    - FLT3/NPM1, BCR-ABL1, +/- PML-RAR
  - Comprehensive profiling by NGS:
    - myeloid gene panel

Favorable Prognostic Factors:

- Ability to achieve complete remission
  - Represents single most important factor related to improved survival
  - Defined as four weeks of normalized peripheral blood counts, plus absence of peripheral blasts
  - Bone marrow cellularity over 20% with trilineage maturation and less than 5% blasts
  - Absence of Auer rods and extramedullary leukemia

Favorable Prognostic Factors:

- Complete remission after single induction cycle confers longer remissions
- Rapid disappearance of blasts from blood after institution of therapy
- Under 1% blasts in bone marrow at time of complete remission
- Presence of t(8;21) of M_2, t(15;17) of M_3, or inv(16) of $M_{4\ Eo}$

Poor Prognostic Factors:

- Older age at diagnosis
  - Age over sixty years influences ability to survive induction (*cf.* intercurrent disease)
  - Associated with resistant disease (*cf.* increased expression of multi-drug resistant gene product)

    Note: *P*-Glycoprotein actively extrudes variety of structurally distinct compounds
- Poor performance status (independent of age)
- Antecedent myelodysplasia

Poor Prognostic Factors:

- Prolonged symptomatic interval before diagnosis
  - Strongly associated with lower complete remission rate and shorter survival
  - Responsiveness to chemotherapy declines steadily as duration of antecedent disorder increases
- High leukocyte count or blast count at presentation

Poor Prognostic Factors:

- Unfavorable cytogenetics
  - Complex karyotypic abnormalities
  - Monosomies of chromosome 5 or 7
  - Deletions of long arm of chromosome 5
  - Abnormalities of chromosome 3 [inv(3)] or 12p fail to achieve complete remission with standard induction
- AML after treatment with cytotoxic agents and/or irradiation for other malignancies remains extremely difficult to treat successfully

Issues in Supportive Care:

- Heart disease complicates treatment due to large amounts of intravenous fluids, antibiotics, transfusions, hydration, and parenteral nutrition required
- Previous herpes simplex infections provides justification for prophylactic administration of acyclovir
- In premenopausal females, suppress menses until thrombocytopenia resolves

Issues in Supportive Care:

- Prior transfusions and previous pregnancies predict for difficulties with adequate platelet increments and herald occurrence of reactions
- Provide adequate blood bank support
  - Administer CMV-negative blood products to sero-negative candidates for allogeneic bone marrow transplant
  - Prophylactic transfusions of Platelets (SDP, RDP)

Treatment: Supportive Care

- Infectious complications represent major cause of morbidity and death in induction and/or post-remission chemotherapy
  - Prevent oral candidiasis
  - Prevent reactivation of latent herpes infections
  - Initiate broad-spectrum antibacterial and antifungal agents with fever to reduce mortality
  - Know Institution bacterial pattern and resistances

Treatment: Induction Chemotherapy

- Left untreated, natural history of AML involves death within weeks to months from infection and/or hemorrhage
- Represents profoundly myelosuppressive therapy with intent to achieve complete remission
  - Affords greatest potential for eradication of leukemic clone and for restoration of normal hematopoiesis
  - During resultant marrow aplasia, "clonal competition" occurs as normal residual progenitors gain growth advantage and re-establish polyclonal hematopoiesis

Treatment: Induction Chemotherapy

- Cytotoxic therapy
  - Markedly decreases number of cells in leukemic clone (typically in order of 10^{12} at diagnosis)
  - Eliminates block in differentiation
  - Rapidly clears leukemic cells from peripheral blood with subsequent marrow aplasia (typically reduces leukemic burden by about 10^3 cells)
- Post-remission therapy essential to achieve prolonged disease-free survival (*cf.* residual cells)

Treatment: Induction Chemotherapy

- Most commonly used combination to induce complete remission (in patients other than M_3) involves cytarabine and anthracycline ("7+3")
- Cytarabine represents cell cycle S-phase specific antimetabolite
  - Phosphorylation to triphosphate by deoxycytidine kinase permits incorporation into DNA and interference with DNA polymerase (synthesis)
  - Administered as continuous intravenous infusion at 100 to 200 mg/m^2/d on days 1 through 7

Treatment: Induction Chemotherapy

- Anthracyclines intercalate into DNA and interact with topoisomerase II to produce DNA strand breakage
  - Daunorubicin administered at 45 to 60 mg/m^2 IV QD for days 1 through 3
  - Idarubicin administered at 12 to 13 mg/m^2 IV QD for days 1 through 3
  - Other potential agents include mitoxantrone, amsacrine, rubidazone, and aclarubicin

Treatment: Induction Chemotherapy

- Idarubicin
  - Associated with more rapid eradication of leukemia and less chemoresistance (able to circumvent MDR)
  - Benefits counterbalanced by higher toxicity (deaths in induction)
  - Cardiotoxicity remains less common in patients treated with cumulative doses up to 290 mg/m^2
    - Much higher than 150 mg/m^2 attained in standard protocols
    - At cumulative doses of 290 mg/m^2, probability of idarubicin-related cardiomyopathy remains under 5%

Treatment: Induction Chemotherapy

- Examination of bone marrow on day fourteen evaluates magnitude of cytoreduction and defines return of normal hematopoiesis or leukemia cells
- Unequivocal persistence or recurrent leukemia mandates re-induction therapy
  - Use of NOVE chemotherapy given unless cardiotoxicity

Treatment: Induction Chemotherapy

- Expect complete remissions in 65 to 75% of adults with *de novo* AML after "7+3" regimen
- 67% achieve complete remission after single course of therapy, whereas 33% require two courses to achieve complete remission
- For patients who fail to achieve complete remission,
  - 50% demonstrate resistant disease
  - 50% die from complications of marrow aplasia or impaired recovery of normal stem cells

Reasons for Treatment Failure Vary Based on Patient Age:

- With sophisticated supportive care, remains relatively uncommon for patients under age fifty to die from complications of treatment
- Over 75% of patients with AML exceed sixty years of age
- Unfavorable prognostic factors increase with age (*cf.* cytogenetics, drug resistance, myelodysplasia)
  - Inability to tolerate intensive chemotherapy
  - Inability to fight intercurrent medical conditions

Biology of Disease Changes with Age:

- AML in younger patients typically evolves from committed stem cell

  Note: Both platelets and erythrocytes derive from normal stem cells

- AML in older patients typically evolves from more primitive pluripotent stem cell (CD_{34}^{+})

  Note: All hematopoietic cells derive from leukemic clone

Biology of Disease Changes with Age:

- After cytotoxic chemotherapy, normal (nonclonal) hematopoiesis remains more likely to be restored in younger than older patients
- Limited self-replicative ability of more mature CFU-GM and persistence of normal stem cells in younger patients allow restoration of normal hematopoiesis
  - Restoration never occurs when pluripotent stem cell undergoes neoplastic transformation

Biology of Disease Changes with Age:

- Elderly demonstrate higher incidence of
  - Antecedent myelodysplasia and secondary leukemia
  - Unfavorable karyotype (32%)
  - Immature blasts (CD_{34}^{+} cells)
  - MDR expression (71%) and functional efflux (58%)
- Chances of complete remission reach
  - 81% if *MDR1*$^{-}$ and favorable cytogenetics co-exist
  - 12% if *MDR1*$^{+}$ and unfavorable cytogenetics or secondary disease co-exist

Biology of Disease Changes with Age:

- Elderly demonstrate overall probability of complete remission of 50% and disease-free survival of 20%
  - Age under eighty years
  - Good physical condition
  - Primary rather than secondary AML
  - Absence of cytogenetic abnormalities
  - Absence of leukocytosis at diagnosis

Biology of Disease Changes with Age:

- Despite inferior results from intensive therapy,
  - Significantly longer overall survival achieved (21 weeks versus 11 weeks)
  - Prolonged survival at thirty months (13% versus 0%)
  - Improved quality of life

  when compared with observation and supportive care

Biology of Disease Changes with Age:

- Results of chemotherapy in patients over eighty or in very poor general condition remain so poor that such patients merit only attenuated dose chemotherapy or purely palliative therapy
- Multi-drug resistance (*MDR1*) gene localized to chromosome 7 band q21.1
  - 170 kDa gene product (*P*-glycoprotein) promotes efflux of structurally dissimilar large hydrophobic molecules

Complete Remission Rate Based on *MDR* and CD_{34} Status:

Phenotype	CR Rate
MDR1$^-$ / CD_{34}^-	72%
MDR1$^+$ / CD_{34}^- *or* *MDR1*$^-$ / CD_{34}^+	53%
MDR1$^+$ / CD_{34}^+	38%

del(5q) and del(7q) highly associated with *MDR1*$^+$ / CD_{34}^+ phenotype

Treatment: Post-Remission Therapy

- Induction of durable first complete remission remains critical to long-term disease-free survival
- Post-remission therapy seeks to eradicate residual leukemic cells (*cf.* 10^9 remain after induction chemotherapy), prevent relapse, and prolong survival

Treatment: Post-Remission Therapy

- Consolidation and intensification describe therapies of equal or greater intensity, respectively, than regimen used in initial induction therapy
- Maintenance refers to lower-dose therapy administered on intermittent basis for months to years, and frequently at doses that fail to produce significant myelosuppression

Post-Remission Therapy: High-Dose Cytarabine

- Cytarabine demonstrates dose-response effect
  - Involves administration of at least two to four courses (3,000 mg/m^2 IV Q12h on days 1, 3, and 5)
- Prolongs complete remission and increases disease-free survival at four years to 30 to 40%
  - Especially beneficial for patients with favorable and normal cytogenetics
  - Long-term results for patients under forty years resemble autologous or allogeneic bone marrow transplant

Secondary AML:

- Complete remissions achieved in only 20 to 30% of secondary leukemias
- Responses improve if diagnosis not preceded by pancytopenia or myelodysplasia
- Very occasionally demonstrate favorable cytogenetics

Treatment: Acute Promyelocytic Leukemia

- All-*trans*-retinoic acid causes brief proliferation of abnormal clone followed by maturation, terminal differentiation, and apoptotic death of leukemic clone
- Lysis of leukemia cells worsen DIC
- DIC ameliorated by ATRA within 48 hours
- ATRA alone insufficient for long term control of disease

Treatment: Acute Promyelocytic Leukemia

- Daily administration of all-*trans*-retinoic acid during induction chemotherapy
  - Promotes terminal differentiation of promyelocytes
  - Reduces complications of cytotoxic therapy
  - Reduces likelihood of relapse
  - Improves outcome in patients with t(15;17)
    - Complete remission over 80% in both previously untreated and relapsed disease
    - Disease-free survival of 87% at one year, 70% at two years, and 67% at three years

APL Induction

- ATRA Day 1 until remission confirmed
- Idarubicin 12/mg/m^2 D2, 4, 6, & 8
- CNS Prophylaxis if wbc >10,000 @ presentation D10 – 12 and with each consolidation
- Decadron 10 mg bid if WBC > 10,000 x 3 days

Adverse Effects: All-*trans*-retinoic acid

- Headache and pseudotumor cerebri
- Xerosis, xerostomia, pruritus, and chelitis
- Bone pain and arthralgias
- Hypertriglyceridemia
- Transient increases in serum aminotransferases, alkaline phosphatase, and bilirubin
- Leukocytosis
- Teratogenicity (marked craniofacial and limb deformities)

Adverse Effects: Retinoic Acid Syndrome

- Represents "capillary leak" syndrome
- Occurs in 20 to 30% treated with ATRA
- Risk increased by high leukocyte count
- Characterized by fever, chest pain, dyspnea, pulmonary infiltrates, and progressive hypoxemia within first three weeks of therapy
- Progresses to peripheral edema, pleural and pericardial effusions, hypotension, and renal failure

Adverse Effects: Retinoic Acid Syndrome

- Rapidly fatal unless reversed with aggressive and early initiation of glucocorticoid therapy, oxygen, and supportive care
- Initiation of dexamethasone 10 mg IV BID for at least three days at first onset of symptoms arrests progression and markedly reduces mortality

APL Consolidation

- Stratify according to risk
- Low Risk (WBC<10 and Pl >40,000)
- Intermediate Risk (WBC<10 and Pl <40,000)
- High Risk (WBC>10 and Pl <40,000)
- Each includes atra and anthracycline
- Consolidation starts once PMN>1000 & Pl >100,000

APL Maintenance

- Confirm Molecular remission
- Mercaptopurine 50 mg/m^2 daily
- Methotrexate 15 mg/m^2 IM once weekly
- ATRA 45 mg/m^2/day in bid dosing D 1- 15 every 3 months
- Bone marrow and pcr q3months for 2 years and then q6m for 3 years

Post-Remission Therapy: Bone Marrow Transplantation

- Associated with relapse-free survival rates in excess of 40% in recipients of autologous bone marrow transplants in first remission
- Transplantation in second or third remission associated with apparent cure rates in 20%
- Disease-free survival at four years
  - 30% for chemotherapy alone (high-dose cytarabine)
  - 48% for autologous bone marrow transplantation
  - 55% for allogeneic bone marrow transplant

Post-Remission Therapy:
Allogeneic Bone Marrow Transplantation

- Suitable HLA-matched donors exist for less than one-third of potential recipients
- Applicability severely limited by patient age
  - Offered only to patients under fifty or fifty-five years (*cf.* median age of sixty-five years)
  - Mortality from immunosuppression (e.g.: PCP, CMV) and graft-versus-host disease increases with age

Post-Remission Therapy:
Allogeneic Bone Marrow Transplantation

- Use of partially mismatched or matched unrelated donors associated with considerable increase in incidence of severe graft-versus-host disease
- Substantial component of antileukemic effect correlates with occurrence of severity of graft-versus-host disease
- 10 to 20% of patients develop significant symptoms and impairment of performance status due to chronic graft-versus-host disease

Post-Remission Therapy:
Allogeneic Bone Marrow Transplantation

- Attempts to attenuate graft-versus-host disease with immunosuppressive agents associated with decrease in toxicity and increase in relapse rate
- Results in durable long-term survival in 40 to 60% when administered in first complete remission (relapse rates between 10 and 20%)
- Consider allogeneic bone marrow transplant for suitable candidates with HLA-compatible donor *OR* reserve for treatment of relapse

Post-Remission Therapy:
Autologous Bone Marrow Transplantation

- Involves myeloablative treatment supported by autologous stem cell reinfusion
  - Harvest and cryopreserve source of future hematopoietic reconstitution in first remission
- Achieves disease-free survival rates of 40 to 50% with lower toxicity and higher relapse rates (50 to 60%) when compared to allogeneic transplant
- Equivalent to high-dose cytarabine in terms of overall survival (despite decreased relapse and increased treatment-related morbidity)

Relapse:

- Recommend same chemotherapy for patients with longer first complete remissions (over twelve months) due to drug-sensitive disease
- Long-term disease-free survival requires treatment with additional and different agents, or bone marrow transplantation
- Salvage regimens for relapsed disease (as well as for initially refractory disease) such as FLAG are commonly used

Relapsed and Refractory Disease:

- Response rates very low in patients with primary refractory leukemia (inability to induce complete remission after two attempts at induction)
- Short initial complete remission duration or relapse during post-remission chemotherapy implies small likelihood of sustained benefit from re-induction therapy
  - Intensive therapy often shortens life

Case 3

- A 63 year old male presents with fever, fatigue, general malaise. He is bleeding from his nose and oral mucosa. He has multiple bruises and petechiae. He complains of a sore throat and is experiencing more anginal symptoms.
- His temp is 39 HR 110 BP 95/60
- Diaphoretic, No LN or splenomegaly
- Gingival hyperplasia

Case 3 LAB

- Hb 65 MCV 90
- WBC 110,000 95% Blasts + Auer rods
- Platelets 10,000
- PT 1.4 PTT 48
- Fibrinogen 1.0 Dimers +
- Uric Acid 800 LDH 3X normal
- Creatinine 150 Potassium 2.8
- Liver tests Normal
- EKG non specific changes

Case 3 : AML

- Priorities
- ABC
  - Early septic shock
- Febrile Neutropenia
- Transfusion
  - Packed cells, platelets, DIC management
- Cardiac Status

AML Management

- Supportive Care
  - Bowel care
  - Mouth care
  - Diet
  - Uric acid
  - Potassium
  - Transfusion support
  - Psychological support / social services

AML Management

- Leukostasis
- Tumor Lysis
- DIC
- Specific Therapy
  - Induction
  - Consolidation
- BMT