MEDICINE-HEMATOLOGY NEET-SS

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AML

Introduction

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Features :

Acute myeloid leukemia (AML) is a neoplasm characterized by :

- Infiltration of the blood, bone marrow, and other tissues.
- Proliferative, clonal, poorly differentiated cells of hematopoietic system.
- 1.3% of all cancers.
- 31% of all acute leukemias.
- But, 62% of all leukemic deaths.
- AML is the most common acute leukemia in older patients, with a median age at diagnosis of 67 years.

Causes :

- Idiopathic (most common).
- Genetic predisposition.
- Radiation.
- Chemicals/other occupational exposures → Benzene, chloramphenicol, phenylbutazone.
- Drugs :
  i. Alkylating agents → Latency period of 5 yrs (Chr 5 & 7).
  ii. Topoisomerase-II inhibitors → Latency period of 1-3 yrs (Chr 11q23).

Classification of AML :

WHO 2016 myeloid neoplasms with germline predisposition :

MN with germline predisposition :

- AML with germline CEBPA.
- MN with germline DDX41.

MN with germline predisposition + pre-existing platelet disorder :

- MN with germline RUNX1.
- MN with germline ANKRD26.
- MN with germline ETV6.

MN with germline predisposition + other organ dysfunction :

- MN with germline GATA2.
- MN with BM failure syndromes.
- MN with telomere biology disorders.
- MN with Down/Noonan syndrome.

Down syndrome associated AML :

- Age <4 years.
- Acute megakaryoblastic type.
- Mutation of GATA 1 gene.

Pre malignant states :

	CHIP or ARCH	IDUS	ICUS
Mutations	+	-	-
Dysplasia	-	+	-
Cytopenias	-	-	+

- Mutations in DNMT3A, TET2, ASXL1,DTA has 10x risk of haematological malignancy and increased risk of CV mortality.
- ARCH : Age-related clonal hematopoiesis.
- CHIP : Clonal hematopoiesis of indeterminate potential.
- ICUS : Idiopathic cytopenia of undetermined significance.
- IDUS : Idiopathic dysplasia of undetermined significance.

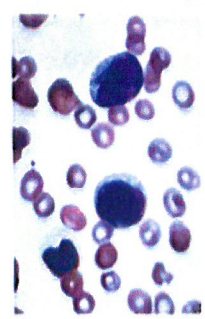
Diagnosis of AML

00:04:39

Case scenario :

A 50 year old man with fatigue and gum bleed since 2 weeks, CBC :7.0 / 1.25 lac / 15,000, peripheral smear reports 80% atypical cells (Shown in panel on right),- flow cytometry shows cells +ve for CD45 dim, cMPO+, CD34+, CD13+, CD33+, CD117+.

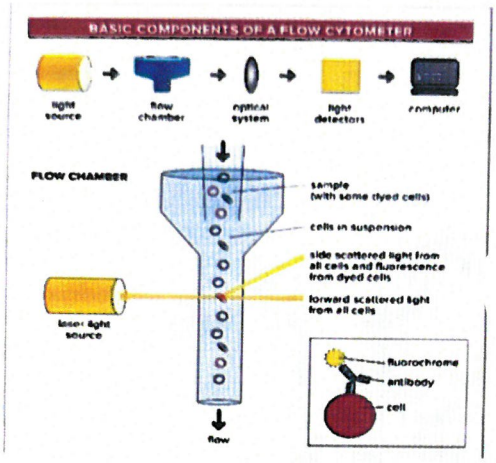
Diagnosis is AML.



Peripheral smear

Flow cytometry/immunophenotyping :

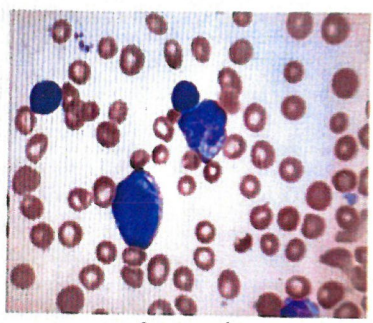
- uses antibodies against specific proteins on surface of cells to differentiate leukemic cells from normal cells.
- Side scattered indicates granularity, forward scattered indicates size.



Flow cytometry

Auer rods :

- Auer rods are rod-shaped crystalline structures derived from the primary granules of myeloid cells.
- Auer rods are of considerable diagnostic importance since they indicate both the lineage and the neoplastic nature of the condition observed.



Auer rods

Assignment of lineage :

WHO 2008 Acute leukemias of ambiguous lineage :

Lineage	Requirements
myeloid.	myeloperoxidase (flow cytometry, immunohistochemistry or cytochemistry) or monocytic differentiation (Diffuse positivity for NSE or atleast two of the following : CD11c,CD14,CD36,CD64,lysozyme.
T.	Cytoplasmic CD3 (Flow cytometry with antibodies to CD3 epsilon chain) or Surface CD3.
B.	Strong CD19 and strong expression of atleast one of the following : CD79a, cytoplasmic CD22, CD10. or Weak CD19 and strong expresion of atleast two of the following : CD79a, cytoplasmic CD22, CD10.

WHO 2016 classification :

It is based on :

- Clinical presentation.
- morphology.
- Cytogenetics.
- molecular features.

Diagnosis :

Bm (or blood) blast count ≥20%, except for AML with recurrent genetic abnormalities.

i. t(15;17).
ii. t(8;21).
iii. Inv(16) or t(16;16).

Acute myeloid leukemia (AML) 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*
Acute promyelocytic leukemia 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, not otherwise specified (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 classification

Association of chromosomal abnormalities with specific features :

- Inv(16) (p13.1q22) with abnormal Bm eosinophils.
- t(8;21) (q22;q22) : Slender Auer rods, CD19+, increased normal eosinophils, myeloid sarcomas.
- t(15;17) : DIC.
- t(9;11) (p22;q23), other 11q23 abn : monocytic features, Bm involvement.

- NPM1 mutation especially when co-occurring with FLT3 mutation : "Cup-shaped" nuclear morphology, high WBC count.
- t(8;21) and t(15;17) : Younger age.
- Del5q, del7q, TP53 mutation : Older age.

APML

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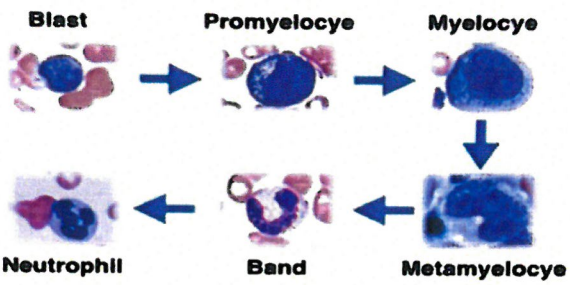
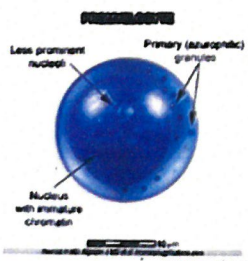
A subtype of AML. There is block in myeloid differentiation at the promyelocyte level.

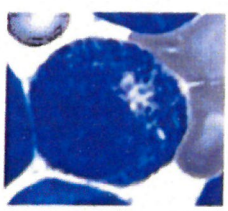


myeloid differentiation

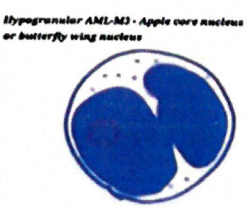
Peripheral smear findings :

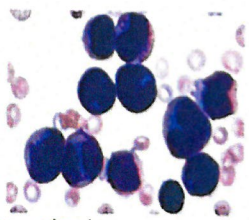
- Normal promyelocyte : Less prominent nucleoli, Primary (azurophilic) granules, nucleus with immature chromatin.
- Abnormal promyelocyte : Apple core/butterfly wing nucleus, prominent violet granules in cytoplasm.
- Pathognomic finding of APML : Faggot cells → Bunch of auer rods.



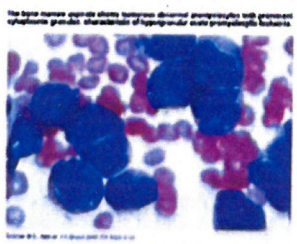


Normal promyelocyte.



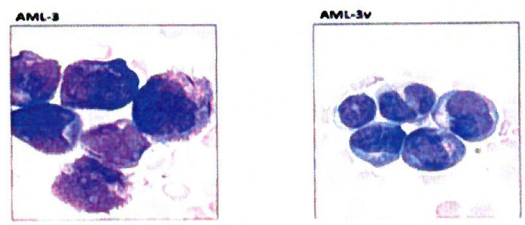


Abnormal promyelocyte.



Faggot cell.

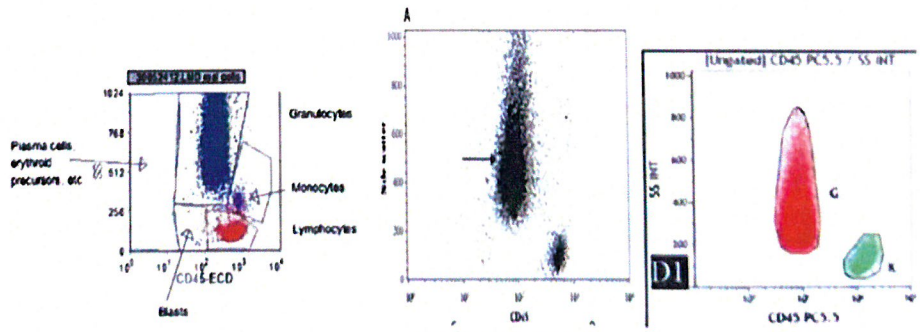
Hypergranular or typical APL (m3).	Hypogranular or microgranular APL (m3v).
60 to 70% of cases.	Leukocytosis.
Low white blood cell count.	Numerous abnormal promyelocytes readily identified on aperipheral blood smear.
Abnormal promyelocytes with numerous red to purple cytoplasmic granules that are typically darker and larger than normal neutrophil granules.	Irregular nucleus and granulations sparser and finer compared with the hypergranular form.
Identifiable faggot/matchstick cells with numerous auer rods.	Faggot cells with multiple auer rods less commonly seen.



APML.

Typical characteristics in flow cytometry :

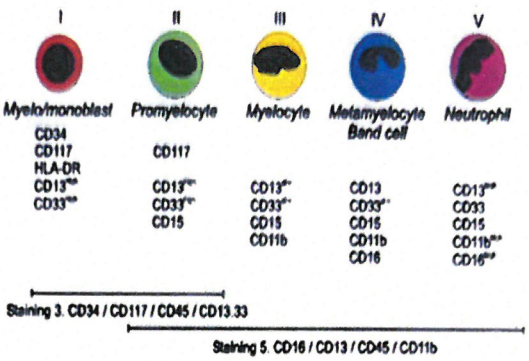
- Intense MPO positivity.
- Autofluorescence on CD45 on X axis and side scattered cells on the y axis.



Autofluorescence.

MPO positivity.

- Flow cytometry pattern in APML :
  - i. HLA DR CD34-.
  - ii. CD13+ CD33+ CD117+.
  - iii. CD11b-.



Flow cytometry in APML.

Pathogenesis :

Pathognomic of APML is 15/17 translocation/PML RARA.

This translocation was given by Janet rowley M.D. (1925 - 2013).

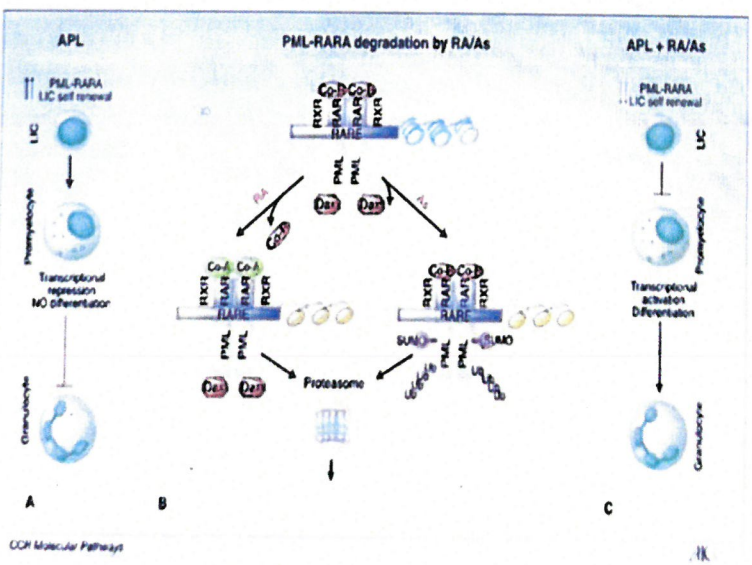
Normal cellular functions :

RARA :

- RAR-alpha interacts with RXR .
- Normal RAR-a-RXR heterodimer recruits corepressor (CoR) or coactivators (CoA) complexes at the chromatin level to differentially regulate transcription of its target genes.

PML :

- Present in specific nuclear structures called nuclear bodies (NBs).
- Promotes apoptosis, and acts as a tumor suppressor.



PML RARA gene pathogenesis.

Mutations :

- NPM1, biallelic CEBPA → Good prognosis.
- FLT3 mutations → Either ITD (bad prognosis) or TKD (uncertain prognosis).

- FLT3-ITD → Occurs preferentially in CN-AML.
- FLT3 allelic ratio (number of mutated alleles to wild-type alleles) is more relevant (Allelic ratio is determined by DNA-fragment length analysis. AUC of FLT3-ITD / AUC of FLT3-wild type).
- Ratio <0.5 – low allelic ratio (AR) → Good prognosis.
- Ratio >0.5 – high allelic ratio → Bad prognosis.

Clinical features of AML

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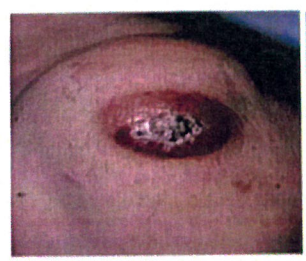
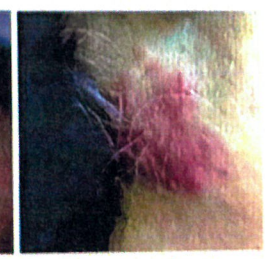
Salient features :

- Fatigue (50%).
- Anorexia and weight loss .
- Fever with or without an identifiable infection (10%).
- Signs of abnormal hemostasis (5%) :
  Bleeding , easy bruising.
- Petechiae.
- Bone pain.
- Lymphadenopathy.

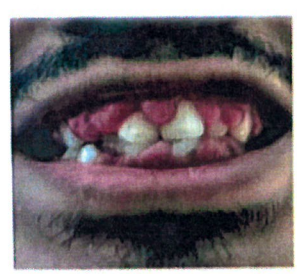
	Leukemia cutis.	Sweet syndrome.
Location.	Trunk.	Face,neck,arms.
Tenderness.	No.	Yes.
Biopsy.	Infiltrate of blasts; Diffuse dermal infiltrate with sparing of upper dermis (Grenz zone).	Infiltrate of neutrophils; Diffuse/band like dermal infiltrate.
Rx.	Same as underlying disease.	Steroids.

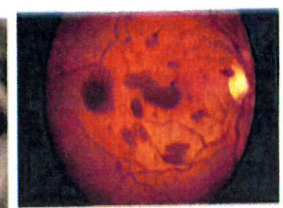


Leukemia cutis.



Sweet syndrome.





AML features.

Myeloid sarcoma

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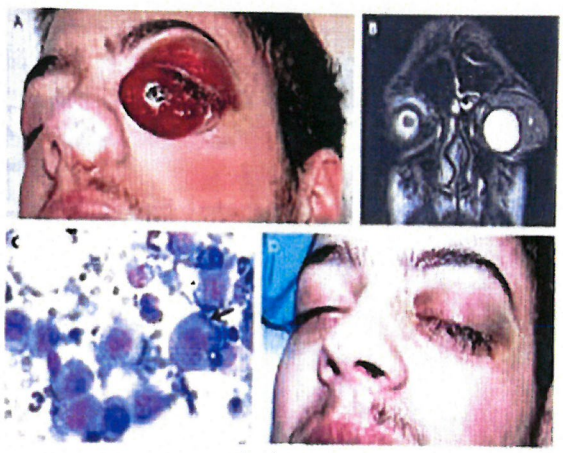
General features :

- Extramedullary collections of myeloblasts.
- Skin, LN, GIT, soft tissue, and testis.
- Association with monosomy 7, trisomy 4, trisomy 8, 11q23 rearrangement, inversion[16], t[8;21].
- may precede or coincide with blood and/or BM involvement by AML.
- MS patients typically develop blood and/or BM involvement quickly thereafter and cannot be cured with local Rx (radiation or surgery) alone.



myeloid sarcoma

Risk stratification of AML

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ELN 2017 risk stratification of AML :

Complex CTG :

>=3 unrelated CTG abn [in absence of t(8;21), inv 16, t(6;9), t(9;11), inv(3), AML with BCR-ABL1].

Monosomal karyotype :

- 1 monosomy (except loss of X or Y) + 1 additional monosomy.
- 1 monosomy + 1 additional structural CTG abn (except CBF AML).

t(9;11) + adverse risk mutations : Count it as t(9;11)

RUNX1, ASXL1, TP53 should not be counted for prognostication, if they occur with favourable risk CTG.

RISK CATEGORY[a]	GENETIC ABNORMALITY
Favorable	t(8;21)(q22;q22); *RUNX1-RUNX1T1*
	inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
	Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITD[low]
	Biallelic mutated *CEBPA*
Intermediate	Mutated *NPM1* and *FLT3*-ITD[high]
	Wild-type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD[low] (w/o adverse-risk genetic lesions)
	t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*[c]
	Cytogenetic abnormalities not classified as favorable or adverse
Adverse	t(6;9)(p23;q34.1); *DEK-NUP214*
	t(v;11q23.3); *KMT2A* rearranged
	t(9;22)(q34.1;q11.2); *BCR-ABL1*
	inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2, MECOM(EVI1)*
	−5 or del(5q); −7; −17/abn(17p)
	Complex karyotype,[e] monosomal karyotype[f]
	Wild type *NPM1* and *FLT3*-ITD[high]
	Mutated *RUNX1*[h]
	Mutated *ASXL1*[h]
	Mutated *TP53*[h]

Prognostic factors :

- Patient related.
- Age.
  i. Comorbidities : Inability to give intensive chemo.
  ii. Intrinsically more resistant disease : Higher number of mutations, CHIP & MDS.
- Poor ECOG-PS.

Disease related :

1. Cytogenetics :
   - t(15;17) have a very good prognosis (85% cured).
   - CBF-AML – t(8;21), inv(16) have a good prognosis (55% cured) (exception – KIT mutations).
   - No CTG abnormality → 40% cured.
   - TP53 mutation, complex karyotype, t(6;9), inv(3), or −7 → very poor prognosis.

2. Antecedent MDS/MPN.

3. Cytopenia duration :
   - Lesser CR rate in patients who have had anemia, leukopenia, and/or thrombocytopenia for >3 months before the diagnosis of AML.

4. Hyperleukocytosis (>100,000/microL) : Risk of early CNS bleeding and pulmonary leukostasis.

molecular prognostic markers :

Prognostic molecular markers in AML are not mutually exclusive & often occur concurrently (>80% patients have at least >=2 prognostic gene mutations), the likelihood that distinct marker combinations may be more informative than single markers

	NPM1	FLT3-ITD
Favorable	+	-
Intermediate	+	+
	-	-
Bad	-	+

GENE SYMBOL	GENE LOCATION	PROGNOSTIC IMPACT
Genes Included in the WHO Classification and ELN Reporting System		
NPM1 mutations	5q35.1	Favorable
CEBPA mutations	19q13.1	Favorable
FLT3-ITD	13q12	Depends on allelic ratio and *NPM1* mutational status
Genes Encoding Receptor Tyrosine Kinases		
KIT mutation	4q12	Adverse
FLT3-TKD	13q12	Unclear
Genes Encoding Transcription Factors		
RUNX1 mutations	21q22.12	Adverse
WT1 mutations	11p13	Adverse
Genes Encoding Epigenetic Modifiers		
ASXL1 mutations	20q11.21	Adverse
DNMT3A mutations	2p23.3	Adverse
IDH mutations (*IDH1* and *IDH2*)	2q34 & 15q26.1	Adverse
KMT2A-PTD	11q23	Adverse
TET2 mutations	4q24	Adverse
Deregulated Genes		
BAALC overexpression	8q22.3	Adverse
ERG overexpression	21q22.3	Adverse
MN1 overexpression	22q12.1	Adverse
EVI1 overexpression	3q26.2	Adverse
Deregulated MicroRNAs		
miR-155 overexpression	21q21.3	Adverse
miR-3151 overexpression	8q22.3	Adverse
miR-181a overexpression	1q32.1 and 9q33.3	Favorable

*This table excludes acute promyelocytic leukemia.

Abbreviations: AML, acute myeloid leukemia; ELN, European LeukemiaNet; ITD, internal tandem duplication; PTD, partial tandem duplication; TKD, tyrosine kinase domain; WHO, World Health Organization

Treatment

00:35:35

Pre treatment evaluation :

Diagnosis :

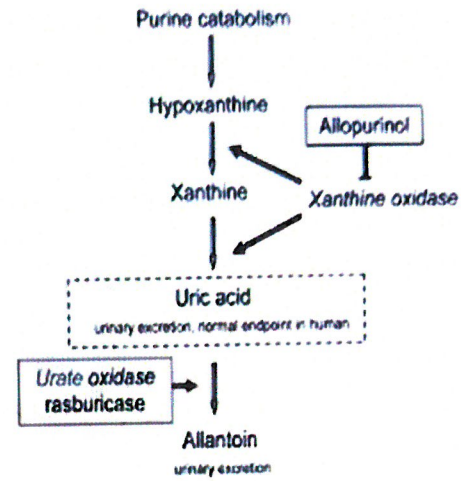
- CBC : median WBC 15,000, 1/3rd - <5K, 20% - >11ac, <5% → Aleukemic leu-

Kemia.

- Platelet <1lac in 75% (1/4th with <25K).
- Bm aspirate, biopsy, flow-cytometry, CTG.

Fitness :

- LFT, RFT (especially uric acid, calcium,
- creat, phosphorus).
- Coagulation – PT, PTT, Fibrinogen, D-dimer.
- Cardiac – Echo or MUGA scan.
- Viral markers.
- Blood grouping.
- Future : HLA matching, cryopreservation of leukemia cells, sperm cryopreservation.



Purine catabolism.

Response assesment :

Definition of CR :

- Achievement of CR is associated with better outcome and longer survival.
- ANC ≥1000/micro L.
- Platelet count ≥100,000/micro L (Hb is not considered in determining CR).
- Bm blasts <5%, without Auer rods.
- Circulating blasts should be absent. Although rare blasts may be detected in the blood during marrow regeneration, they should disappear on successive studies.
- Extramedullary leukemia should not be present.

Principles of treatment :

- Rx divided in 2 parts : Induction & Consolidation.
- Induction therapy : To induce CR.
- Consolidation chemotherapy : Prolong survival and achieve cure.

Induction chemotherapy :

Intensive chemotherapy (ICT) → 7+3 regimen :

- 7 days Ara-C (100-200mg/m2/d continuous infusion) + 3 days Daunomycin (60mg/m2/d).
- CR rates : Young (<60yrs) → 60-80%, Elderly fit → 30-60% CR.
- Rest have induction deaths or drug resistant leukemia.

- Cytarabine : Cell cycle specific (S-phase) becomes phosphorylated intracellularly to an active triphosphate form .Interferes with DNA synthesis.
- Anthracyclines : Cell-cycle non-specific (DNA intercalators),Inhibition of topoisomerase II, leading to DNA breaks.

Consolidation or Post-remission Rx in favourable risk AML : IDAC/HIDAC

- Durable CR-1 is critical to long-term survival in AML.
- Without further therapy after induction, virtually all patients relapse.
- Consolidation Rx is given to eradicate residual leukemic cells to prevent relapse.
- HiDAC (3 g/m2, every 12 h on D 1, 3, 5) or IDAC (1-1.5 g/m2).
- Number of cycles : 2-4.

Consolidation or post-remission treatment in Intermediate or high-risk AML :

- Allogeneic HCT is the best relapse-prevention strategy currently available for AML.
- Why transplant ?
    i. Once AML relapses, it is typically resistant to chemotherapy.
    ii. Hence, allogeneic HCT in CR1 is a favoured strategy.
- Why allogeneic HSCT, if autologous HSCT has less transplant-related mortality ? Relapse rate is less due to graft-versus-leukemia effect.

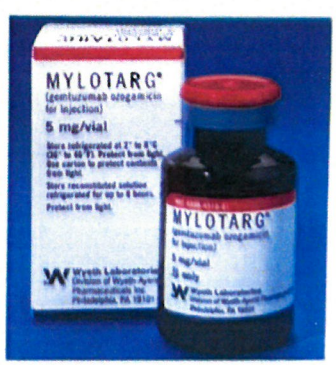
Novel agents :

FDA approvals in 2017 :

- Gemtuzumab ozogamicin.
- Enasidenib.
- Midostaurin.
- CPX351.

Gemtuzumab ozogamicin :

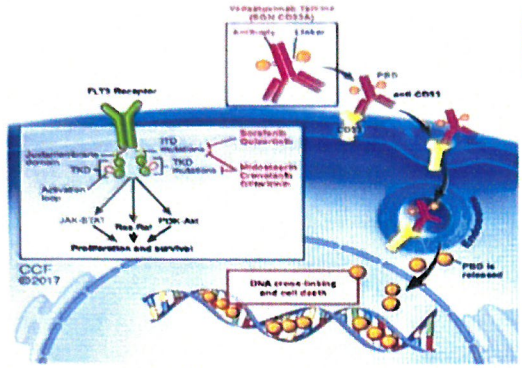
- 1 SEP/ 2017, FDA approved.
- Indications :
    i. Adults with newly diagnosed CD33+ AML.
    ii. >2 yrs with CD33+ AML relapsed / refractory.



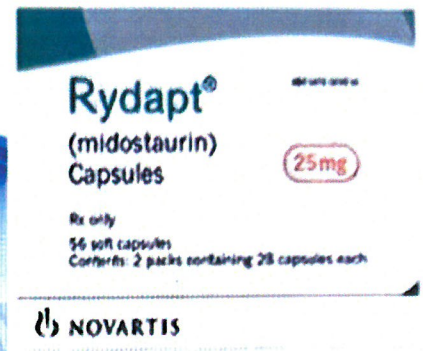
Gemtuzumab ozogamicin

midostaurin :

FLT3 inhibitor.



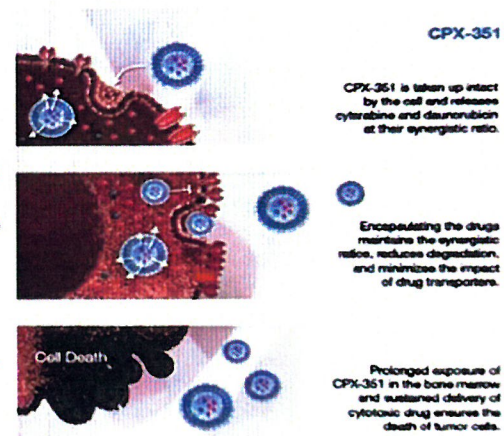
MOA of midostaurin



midostaurin tablet

CPX-35 I: VYXEOS :

- FDA approved for elderly (60-75 years) fit patients with t- AML or AML - MRC.
- A nano scale liposomal co formulation of cytarabine and daunorubicin at a synergistic 5:1 molar ratio.
- Taken up preferentially by human leukemia cells, ensuring intracellular delivery of the optimal dose.
- Hypothesized that preferential uptake into leukemia cells boosts efficacy while maintaining a very favorable non hematological toxicity profile.



CPX 35

Elderly AML :

Elderly vulnerable : Consider lower intensity therapy.

- Hypomethylating agent (decitabine or azacitidine) + Venetoclax
- Low dose cytarabine + Venetoclax
- IDH1 or IDH2 inhibitor, if mutated
- Gemtuzumab single agent.
- preferably investigational therapy.

Elderly frail : Best supportive care/palliative care.

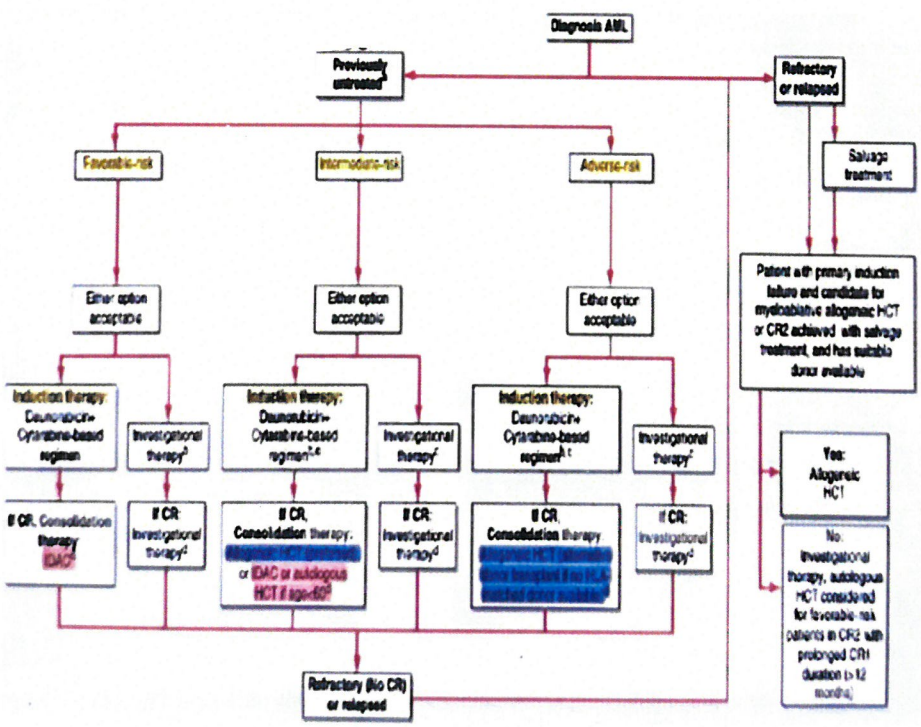
Supportive care :

- Maintain a platelet count above 10,000/micro L.
    i. >20000/micro L - febrile patients and during episodes of active

bleeding.

ii. >50000/microL - hyperleukocytosis.

- Maintain Hb >7-8 g/dL
  i. >7-8 in active bleeding, DIC, or CHF, shock, elderly.
- Leukodepletion : To delay alloimmunization, febrile reactions (FNHTR), CMV.
- Irradiation : To prevent TA-GVHD.
- Antifungal prophylaxis : (Anti-mold agent) Posaconazole.
- FN : Ist line → Antipseudomonal penicillin + Aminoglycoside.
- Empirical vancomycin/teicoplanin - when to add gram positive cover
  i. Catheter-related infection.
  ii. Hypotension or shock.
  iii. Known colonization with methicillin-resistant Staph.aureus (MRSA).
  iv. Skin infections.
  v. Pneumonia.
  vi. Quinolone prophylaxis.
- Empirical antifungals : If fever persists beyond 5 days.
- Growth factors : Useful in consolidation (Post-remission setting).



Treatment layout

Relapsed refractory AML

00:55:36

Treatment :

- Length of CR-1 is predictive of response to salvage chemotherapy treatment

i. If CR-1 >12 months : Better prognosis as a drug-sensitive disease and may respond to same chemotherapy.
ii. Remember : All patients in relapse setting should undergo Allo HSCT in CR2.

- If CR1 <12 months or post-Allo HSCT relapse : Need innovative approaches on clinical trials.

Newer drugs for AML :

- BCL 2 inhibitor : Venetoclax.
- IDH 1 inhibitor : Ivosidenib, IDH 2 inhibitor : Enasidenib.
- Newer FLT3 inhibitors : Sorafenib, Midostaurin, Giltertinib, Quizartinib.
- Hedgehog inhibito : Glasdegib.
- Anti-CD33 : Gemtuzumab oogamycin.
- Liposomal Daunorubicin + cytarabine : CPX-351 (Vyxeos).
- DOTIL inh, HDAC inh, BET inhibitors.

Risk stratification of APML

00:57:47

Sanz stratification :

It includes LR,IR,HR.

- LR : WBC <10, platelet >40.
- IR : WBC >10, platelet >40.
- HR : WBC >10, Platelet <40.

Modified Sanz (LR,HR) :

- WBC <10 vs >10.

Low risk APML :

- Induction : ATRA + ATO is given.
- Consolidation : ATRA + ATO is given.
- Maintainance is not given in low risk APML.

High risk APML :

- Induction : ATRA + ATO+ Anthracyclines.
- Anthracyclines is given to prevent differentiation syndrome.
- Consolidation : ATRA + ATO.
- As per latest guidelines maintainace is not necessary for high risk APML.

Complications of treatment of APML :

ATRA :

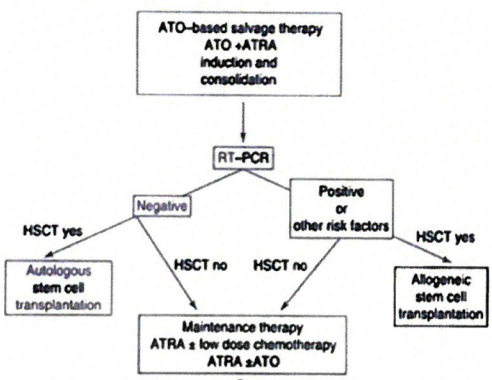
Induces differentiation of leukemic cells with t(15;17).

Differentiation syndrome :

- 25% cases, usually in first 3 weeks of treatment.
- C/F : Fever, fluid retention, dyspnea, chest pain, pulmonary infiltrates, pleural and pericardial effusions, hypoxemia.
- It happens due to adhesion of differentiated neoplastic cells to the pulmonary vasculature endothelium.
- Treatment : Steroids – Dexamethasone 10mg IV BD, ATRA discontinuation temporarily (in renal failure or severe respiratory distress).
- mortality : 10%.
- Prevention : Prophylactic steroids.

Treatment of relapsed APML :

molecular, cytogenetic, or clinical relapse should be salvaged with ATO and chemo +/- ATRA



Treatment of relapsed APML

Latest changes in AML

01:02:46

WHO5 AML with defining genetic abnormalities :

All classes will have <20% blasts except :

- Acute myeloid leukemia with BCR:ABL1 fusion.
- Acute myeloid leukemia with CEBPA mutation.
- Acute myeloid leukemia, myelodysplasia - related

Acute promyelocytic leukaemia with *PML::RARA* fusion

Acute myeloid leukaemia with *RUNX1::RUNX1T1* fusion

Acute myeloid leukaemia with *CBFB::MYH11* fusion

Acute myeloid leukaemia with *DEK::NUP214* fusion

Acute myeloid leukaemia with *RBM15::MRTFA* fusion

Acute myeloid leukaemia with *BCR::ABL1* fusion

Acute myeloid leukaemia with *KMT2A* rearrangement

Acute myeloid leukaemia with *MECOM* rearrangement

Acute myeloid leukaemia with *NUP98* rearrangement

Acute myeloid leukaemia with *NPM1* mutation

Acute myeloid leukaemia with *CEBPA* mutation

Acute myeloid leukaemia, myelodysplasia-related

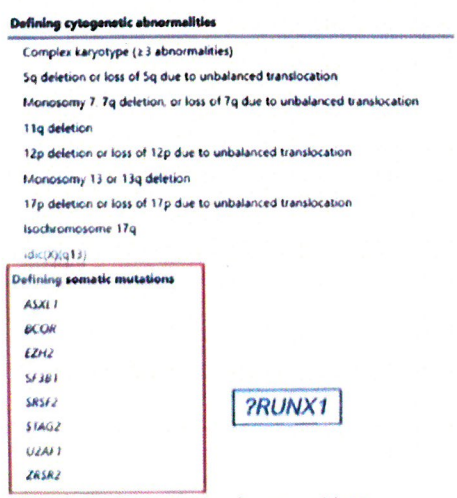
Acute myeloid leukaemia with other defined genetic alterations

WHO5 AML classification

AML - MR (myelodysplasia related):

The diagnosis of AML-MR requires that the following 3 criteria are met:

- ≥ 20% blasts in blood or marrow
- Presence of at least one of the following:
  - i. History of MDS or MDS/MPN.
  - ii. One or more cytogenetic or molecular abnormalities.
- Absence of the following:
  - i. History of exposure to cytotoxic therapy.
  - ii. History of myeloproliferative neoplasm.
  - iii. Criteria for AML with defining genetic abnormalities.
  - iv. Criteria for myeloid neoplasms associated with germline predisposition



Cytogenetic abnormalities

myeloid neoplasms post cytotoxic therapy (MN-pCT) :

- Fulfills criteria for one of the myeloid neoplasms (myelodysplastic neoplasms, myelodysplastic/myeloproliferative neoplasms/acute myeloid leukaemia).
- History of cytotoxic therapy (cytotoxic agents listed below) :

1. Alkylating agents :
   melphalan, cyclophosphamide, nitrogen mustard, chlorambucil, busulfan, carboplatin, cisplatin, dacarbazine, procarbazine, carmustine, mitomycin C, thiotepa, lomustine.
2. Ionizing radiation therapy :
   Large fields containing active bone marrow.
3. Topoisomerase II inhibitors :
   Etoposide, teniposide, doxorubicin, daunorubicin, mitoxantrone, amsacrine, actinomycin.
4. Others :

- Antimetabolites, thiopurines, mycophenolate mofetil, fludarabine.
- Antitubulin agents (usually in combination with other agents) : Vincristine, vinblastine, vindesine, paclitaxel, docetaxel.
- PARPi inhibitors.

Methotrexate has been excluded.

myeloid neoplasms associated with germline predisposition :

Myeloid neoplasms with germline predisposition without a pre-existing platelet disorder or organ dysfunction

- Germline *CEBPA* P/LP variant (CEBPA-associated familial AML)
- Germline *DDX41* P/LP variant[a]
- Germline *TP53* P/LP variant[a] (Li-Fraumeni syndrome)

Myeloid neoplasms with germline predisposition and pre-existing platelet disorder

- Germline *RUNX1* P/LP variant[a] (familial platelet disorder with associated myeloid malignancy, FPD-MM)
- Germline *ANKRD26* P/LP variant[a] (Thrombocytopenia 2)
- Germline *ETV6* P/LP variant[a] (Thrombocytopenia 5)

Myeloid neoplasms with germline predisposition and potential organ dysfunction

- Germline *GATA2* P/LP variant (GATA2-deficiency)
- Bone marrow failure syndromes
  - Severe congenital neutropenia (SCN)
  - Shwachman-Diamond syndrome (SDS)
  - Fanconi anaemia (FA)
- Telomere biology disorders
- RASopathies (Neurofibromatosis type 1, CBL syndrome, Noonan syndrome or Noonan syndrome-like disorders[a,b])
- Down syndrome[a,b]
- Germline *SAMD9* P/LP variant (MIRAGE Syndrome)
- Germline *SAMD9L* P/LP variant (SAMD9L-related Ataxia Pancytopenia Syndrome)[c]
- Biallelic germline *BLM* P/LP variant (Bloom syndrome)

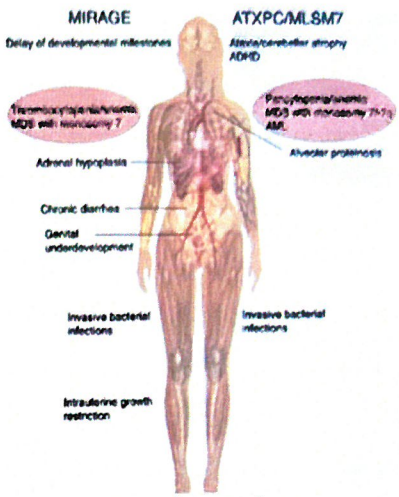
Classification of myeloid neoplasms

MIRAGE syndrome :

Rare disorder characterized by six core features :

- myelodysplasia.
- Infection.
- Restriction of growth.
- Adrenal hypoplasia.
- Genital phenotypes.
- Enteropathy.

It is due to SAMD9 mutation.



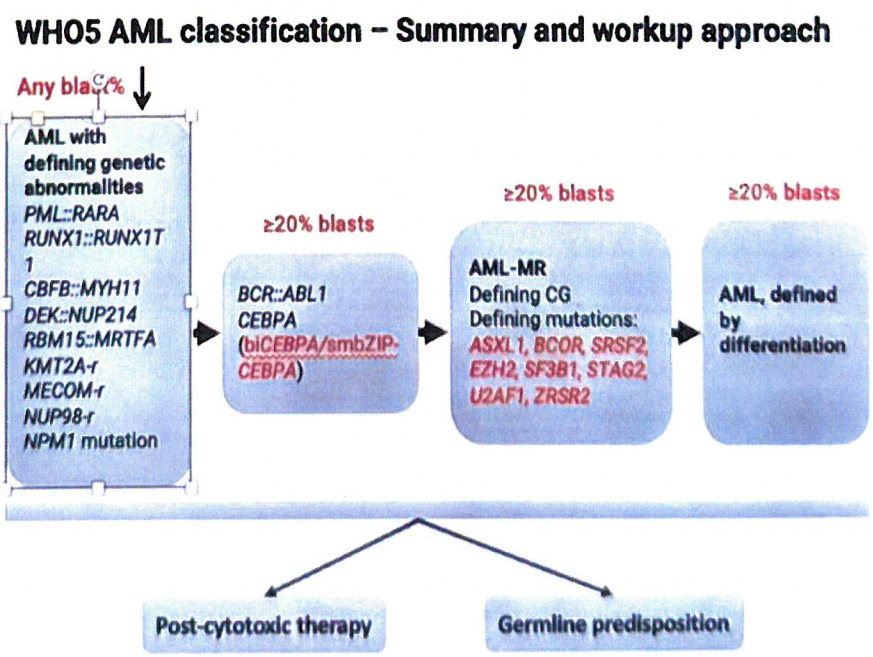
MIRAGE/ATXPC/MLSM7

ATXPC :

Ataxia pancytopenia syndrome due to SAMD9L mutation.

MLSM7 :

myelodysplasia and leukemia syndrome with monosomy 7 due to SAMD9L mutation.



ELN 2022 :

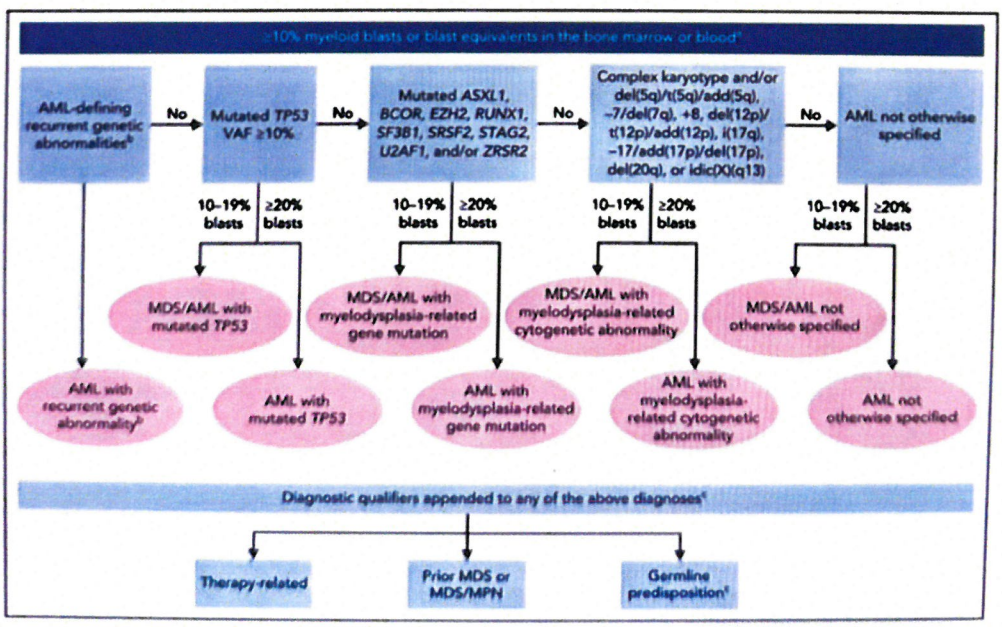
2022 ELN risk categorization

Risk Category	Genetic Abnormality
Favorable	• t(8;21)(q22;q22.1)/*RUNX1::RUNX1T1* • inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB::MYH11* • Mutated *NPM1*[a] without *FLT3*-ITD • bZIP in-frame mutated *CEBPA*
Intermediate	• Mutated *NPM1*[a] with *FLT3*-ITD • Wild-type *NPM1* with *FLT3*-ITD • t(9;11)(p21.3;q23.3)/*MLLT3::KMT2A* • Cytogenetic and/or molecular abnormalities not classified as favorable or adverse
Adverse	• t(6;9)(p23;q34.1)/*DEK::NUP214* • t(v;11q23.3)/*KMT2A*-rearranged • t(9;22)(q34.1;q11.2)/*BCR::ABL1* • t(8;16)(p11;p13)/*KAT6A::CREBBP* • inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/*GATA2,MECOM(EVI1)* • t(3q26.2;v)/*MECOM(EVI1)*-rearranged • -5 or del(5q); -7; -17/abn(17p) • Complex karyotype, monosomal karyotype • Mutated *ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, or ZRSR2* • Mutated *TP53*

Note:

- The ELN AML risk classification has been developed based on data from intensively treated patients and may need modifications for patients receiving less intensive therapies
- Initial risk assignment may change during the treatment course based on the results from MRD analyses

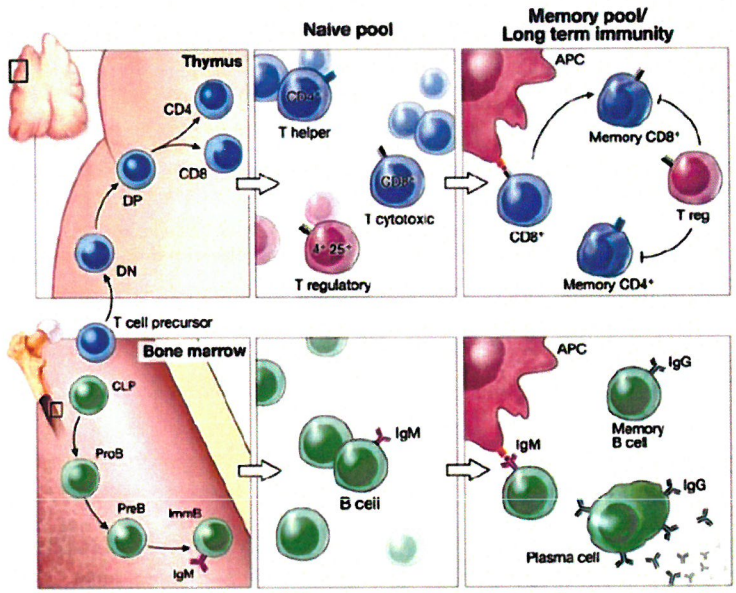
ELN 2022 AML :



ACUTE LYMPHOCYTIC LEUKEMIA

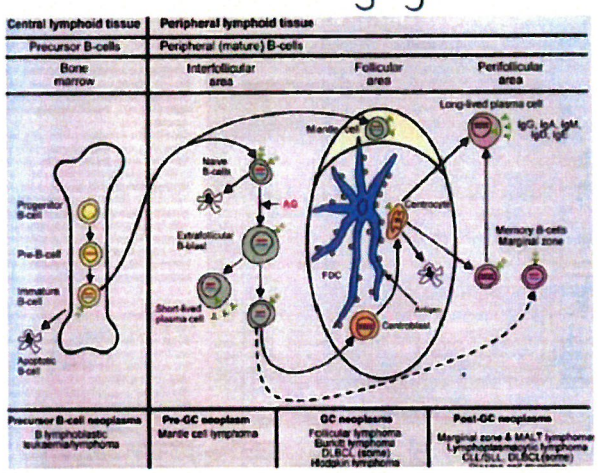
Defenition 00:00:10

Lymphoid development



Initial part of B cell happens in Bone marrow.
Initial part of T cells happenstance in Thymus.

B cell ontogeny



Origin:

Arises from hematopoietic progenitors in bone marrow (BM)
Causes BM infiltration(mc) leading to cytopenias.
Less commonly – presentation due to tumor bulk – LN or

Active space

organomegaly or CNS symptoms.

Leave Feedback

Incidence and Age:

Children: most common malignancy

Peak age: 3–4 years

Adults: incidence 0.7 to 1.8/100,000 per year.

Younger adults: 1–1.5 for the age group 15–24 years, decreasing thereafter.

Elderly people incidence increases to 2.3 for age >65 years.

The frequency of immunological, cytogenetic, and genetic subtypes changes with age.

Ph+ ALL; BCR/ABL translocation is observed in half of elderly B-lineage patients.

Etiology:

Less well known predisposing factors than AML.

Ionizing radiation

Chemicals, including prior chemotherapy.

Congenital Disorders.

Klinefelter's syndrome

Fanconi's anemia(Inherited Bone marrow failure syndrome+ DNA repair syndrome), Ataxia telangiectasia, Bloom's syndrome (DNA Repair Syndromes)

Neurofibromatosis

Down's syndrome: 20x increased incidence of leukemia (ALL in childhood or AML at an older age)

Genetic predisposition: identical twin of a leukemic child has 5x risk of acute leukemia

Infections (implicated in a lymphoid neoplasias)

- Human T-cell leukemia virus I (HTLV-I): Adult T-cell leukemia/lymphoma.
- Epstein-Barr virus: Burkitt's lymphoma (Endemic African type)

Active space

Clinical Presentation

00:08:25

General systemic effects (fever, lassitude, pallor)

C/F due to marrow involvement

- Anemia (fatigue, pallor, dyspnea, CHF)

- Leucopenia (fever, infections)
- Thrombocytopenia (easy bruisability, petechiaes, ICH)

C/F from Lymphoid System Infiltration

- Hepatomegaly
- Splenomegaly
- Lymphadenopathy

C/F of Extramedullary Invasion

- CNS (< 5% of childhood ALL)

Signs and symptoms of parenchymal involvement.

Raised ICP.

- Genitourinary tract (testis, priapism, ovary, kidney)
- GI tract (Typhlitis, bleeding)
- Bone (25% patients have bone pains)
- Skin

B-LBL (Lymphoblastic Lymphoma):

Mediastinal masses are rare.

Extranodal sites- more common

Lymph nodes alone (13 percent)

Osteolytic bone lesions (26 percent), skin (23%), mediastinal or pleural disease (11%),bone marrow (13%), gonads (6%), head and neck (4%), or kidney and digestive system.

Work up

00:11:12

Steps in diagnosis

Acute leukemia – yes or no ?

Peripheral smear (blasts might be seen)

Bone marrow aspirate morphology

Which type of acute leukemia ?

Cytochemistry (NPO- acute myeloid, PAS - ALL, NSE - AML and ALL

Flow-cytometry or immunophenotyping

Prognostication (and treatment choice)

Cytogenetics (conventional and FISH)

Molecular – PCR, NGS

Leave Feedback

TABLE 106-1 Laboratory Values at Diagnosis of Acute Lymphoblastic Leukemia (ALL)

		ALL
NO.		1273*
Initial white blood cell count ($\times 10^9$/L)	<10	41%
	10–50	31%
	>50–100	28%
	>100	16%
Neutrophils ($\times 10^9$/L)	<50–100	12%
	<100,000	16%
Platelets ($\times 10^9$/L)	<20	22%
	21–40	22%
	41–100	29%
	>100	27%
Hemoglobin (g/dL)	<7	20%
	7–9	33%
	>9	47%
Leukemic blasts in peripheral blood	0%	8%
	25–75%	34%
	>75%	36%
Leukemic blasts in bone marrow	<50%	4%
	51–90%	25%
	>90%	71%

Source: Data from three consecutive German Multicenter Trials for Adult ALL (GMALL).

Aleukemic Leukemia where no blasts are seen.

Bone Marrow Examination:

Bone marrow aspirate and biopsy

Bone marrow aspirates are important for :

- Morphology
- Flow-cytometry or immunophenotyping (IPT)
- Cytogenetics – conventional karyotyping
- Molecular panel – PCRs or NGS

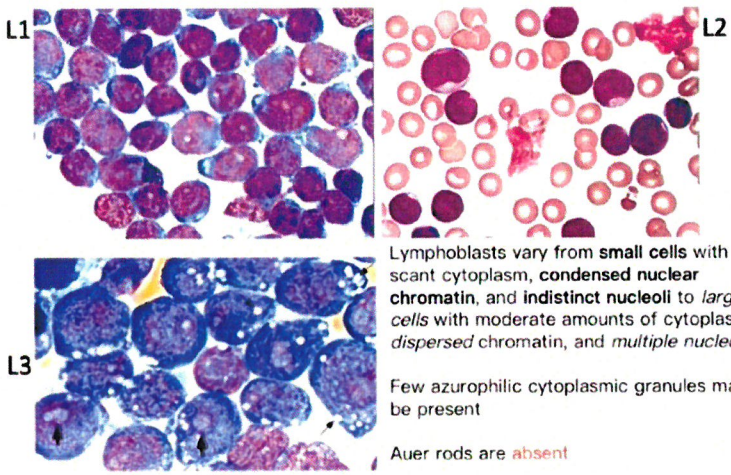
Bone marrow aspirate morphology :

- Heavily packed with blasts >90% of the nucleated cells.
- Normal hemopoietic elements are greatly reduced or absent.

Biopsy: Hypercellularity with replacement of fat spaces and normal elements by infiltration with leukemic cells.

Active space

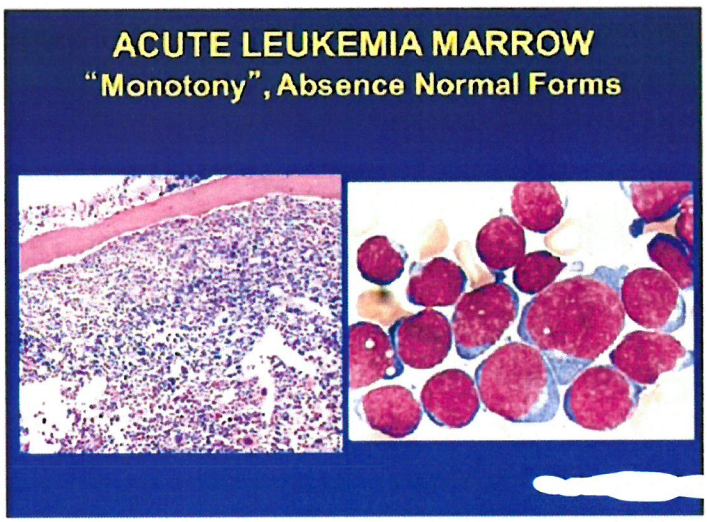
Morphology



Lymphoblasts vary from **small cells** with scant cytoplasm, **condensed nuclear chromatin**, and **indistinct nucleoli** to *larger cells* with moderate amounts of cytoplasm, *dispersed* chromatin, and *multiple nucleoli*

Few azurophilic cytoplasmic granules may be present

Auer rods are absent



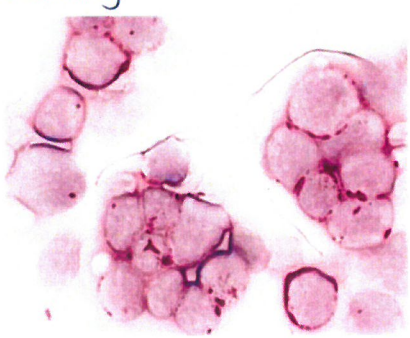
Cytochemistry:

Blasts show "chunky"/ block positivity on periodic acid Schiff (PAS) staining

Variable positivity for NSE, SBB

Universal negativity for myeloperoxidase (MPO)

Block/chunky Positivity



Active space