HEMATOLOGY
&LYMPH SYSTEM

Pathology sheet

Number	9
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Myeloid neoplasms

Note:

Early arrest in the blast cell or immature cell "we call it **acute leukemia**"

Myoid neoplasm divided in to 3 major categories:

1. AML : Acute myeloid leukemia(stem cell with myeloid differentiation)

Acute : arrest in early stages

Leukemia :neoplastic cell in the peripheral blood

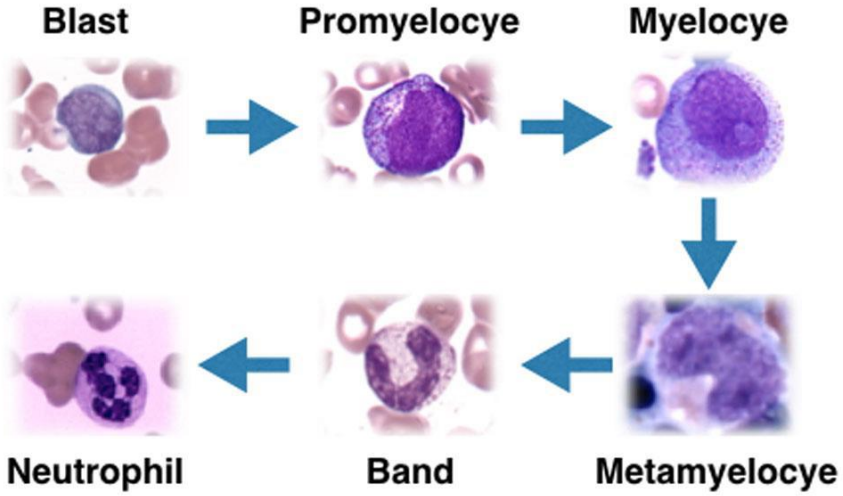
- Age of presentation is around 50 can happen at any age "6months to 70 y "
- Stigmata of **pan**cytopenia "the bone marrow Is replaced completely by neoplastic blasts"
- Splenomegaly
- Rarely as discrete mases Called **myeloid sarcoma**(rare disease around the mouth)
  We don't call it lymphoma?? Because it is not a lymphocytic tumor

Diagnosis depends on:

•Morphology

•Immuneophenotype

•Karyotype (Predictive of prognosis)



In this figure we can see the the stage of differentiation

The blast has a dominant white nucleolus

AML: in the blast or promyelocyte

In MPN and MDS: maturation and differentiation happen

Pathogenesis

•Mutations that result in arresting myeloid cells at an early stage of differentiation
"inability to differentiate "

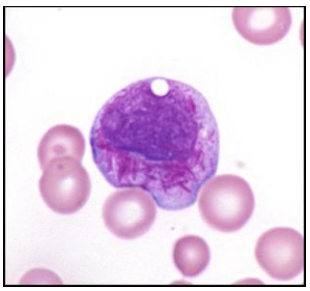
A lot of mutations but please know this example
is acute promyelocytic leukemia
t(15;17) resulting in fusion of RARA with PML (The resulting fusion gene arrests myeloid cells at the promyelocyte stage**)**

the good thing about the fusion gene is that we can design a drugs that target these genes one example is Treatment with **all-trans retinoic acid (ATRA, a vitamin A derivative)** which overcomes this protein and forces the cells to **differentiate** into neutrophils and the remission happen in one week, CURE RATE IS HIGH.
DIC is a possible complication of APL.

Morphology

•At least 20% blasts by definition (you need 20% blasts to call a tumor acute leukemia)

•Auer rods "needle shape structure in the cytoplasm"(it is purple in color or magenta color or deep pink color)



Auer rods are present in myeloblasts, indicating that the tumor is acute myeloid leukemia and not lymphoid, however, its absence does not rule acute myeloid leukemia out. In other words, they are specific for AML but not sensitive.

Class	Prognosis
I. AML With Recurrent Chromosomal Translocations	
AML with t(8;21)(q22;q22); *RUNXT1/RUNX1* fusion gene	Favorable
AML with inv(16)(p13;q22); *CBFB/MYH11* fusion gene	Favorable
AML with t(15;17)(q22;q21.1); *PML/RARA* fusion gene	Favorable
AML with t(11q23;variant); *MLL* fusion genes	Poor
AML with mutated *NPM1*	Variable
II. AML With Multilineage Dysplasia	
With previous MDS	Very poor
Without previous MDS	Poor
III. AML, Therapy-Related	
Alkylating agent–related	Very poor
Epipodophyllotoxin-related	Very poor
IV. AML, Not Otherwise Classified	
Subclasses defined by extent and type of differentiation (e.g., myelocytic, monocytic)	Intermediate

From the above table you have to know:

The general classification "main classes "

Note :the 3rd class (we can diagnose it without tests) previous exposure to =chemo thereby

The cytogenetic translocation carries the best prognosis

Immunophenotype

•CD34 "marker of stem cell or blasts, myeloid or lymphoid

•Myeloid markers
•MPO, CD33, CD13, CD117, CD15

•MPO is the most specific

There is an example of test can't find it in the sides "sorry"

Clinical manifestations

•Very similar to ALL (huge overlap), don't depend on the age DON'T
•Stigmata of **pan**cytopenia
•CNS manifestations are less frequent than ALL

•Treatment with chemotherapy and possibly SCT (stem cell transplantation)

•Prognosis is variable but oveall 5-year survival is~15-30%. (Bad prognosis)

2. MDS (Myelodysplastic syndrome): **The** term *myelodysplasticsyndrome*(MDS) refers to a group of **clonal** stem cell disorders characterized by maturation defects that are associated with ineffective hematopoiesis with **cytopenias** and a high risk of transformation to AML (no cytosis the cells stay in the bone marrow)
   Most cases are idiopathic (Some cases are induced by exposure to alkylating agents or ionizing radiation)
   - Can progress in to AML

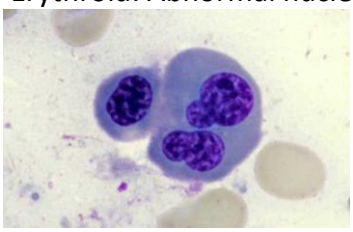
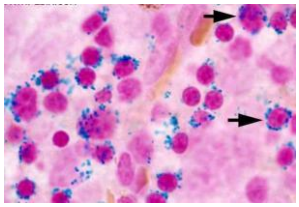
Pathogenesis

involves genetic and epigenetic(change in the gene and not changing the sequence) mutations that result in inability of the stem cells to have effective poeisis. Still able to proliferate and differentiate but **in a disorderly manner!**

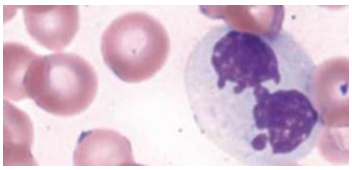
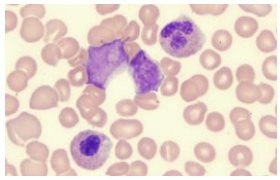
Morphology

•Hypercellular bone marrow

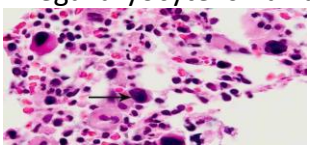
•Dysplastic changes
•Erythroid: Abnormal nuclear contour and iron deposits (ring sideroblasts)

•Myeloid: abnormal segmentation and granulation

•Megakaryocyte: small and monolobed



Clinical manifestations

•Age 50-70

•Cytopenia and its effects (if there is a cytosis it is defiantly not MDS)

•Does not have to be PANcytopenia

•Patients may present with **only** anemia or **only** thrombocytopenia or only leukopenia

•transforms to AML in 10-40% of the cases

•Survival between 9-29 months

3. MPN (Myeloproliferative Neoplasms)

Four major neoplasms

•Chronic myelogenous leukemia

•Polycythemia vera(discussed earlier)

•Essential thrombocythemia

•Primary myelofibrosis

Pathogeneses :

The common pathogenic feature of myeloproliferative neoplasms is the presence of mutated, constitutively activated tyrosine kinases or other acquired aberrations in signaling pathways that lead to growth factor independence (uncontrolled growth). Still have the ability to differentiate

These neoplasms have two fates:

•Spent phase: fibrosis (extensive)

•Blast phase: acute leukemia

Ok let's start:

☒CML (chronic myelogenous leukaemia)

The only neoplasm in which the molecular test is mandatory for diagnosis (BCR-ABL)

Pathogenesis

BCR-ABL translocation t(9;22)

The same as in B-ALL

Present in all cells (B, T, myeloid)

It is a tyrosine kinase that results in uncontrolled proliferation

Does NOT inhibit differentiation

Disease course is marked by excessive production of relatively normal blood cells, particularly granulocytes(basophils) and platelets.

Morphology

•Hypercellular bone marrow

•Splenomegaly with extensive extramedullary hematopoiesis

•High WBC count, often exceeding 100000 (may cause thrombosis)

Clinical manifestations

- Age 50-70
- Nonspecific symptoms of fatigue, weakness
- Dragging sensation in the abdomen due to splenomegaly
- Must be distinguished from "leukemoid reaction"
  - High WBC count secondary to infection or infarction
  - Best done by molecular testing for BCR-ABL
- Slowly progressive disease (Median survival is 3 years without treatment)
- Can progress to accelerated phase(Anemia, thrombocytopenia and additional genetic mutations)

- Progress to blast phase(70% AML 30% ALL)

Myeloid in to lymphoid ?!!!!!! how?
Remember that the mutation is **at the stem cell level**

- Rarely progresses to spent phase with fibrosis

☒Primary myelofibrosis

The hallmark of primary myelofibrosis is :

- **development of obliterative marrow fibrosis, which reduces bone marrow hematopoiesis and leads to cytopenias**
- **extensive extramedullary hematopoiesis**

pathogenesis

JAK2 mutation in ~50-60% of the cases

•Neoplastic cells involve the megakaryocytes (always there is fibrosis)
Secrete fibrogenic factors resulting in extensive fibrosis

- PDGF and TGF-B

•Extramedullary hematopoiesis with marked splenomegaly (may reach 4 KG and can could be felt on the right side)

Morphology

Peripheral blood:
•leukoerythroblastosis same as myelophthisic anemia
Tear drop RBCs

Erythroid precursor cells

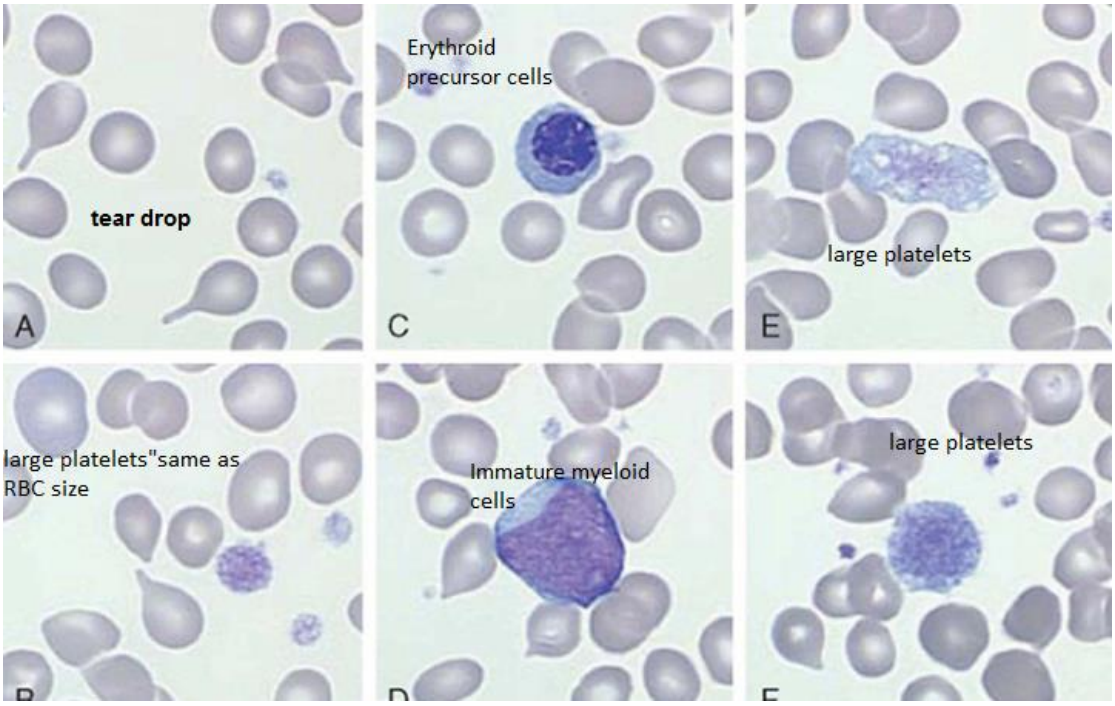
Immature myeloid cells

As you recall this is also found in myelophthisic anemia

•Abnormally large platelets

•Bone marrow:
Severe fibrosis

Abnormally large and clustered megakaryocytes



Clinical manifestations

•Age more than 60

•Anemia and splenomegaly

•Fatigue, weakness and night sweats

•Lab results
•Anemia: normochromic and normocytic

•Leukoerythroblatosis
•Bone marrow is a must for diagnosis (hypercellularity ,fibrosis, cluster of megakaryocytes)
•Median survival is 4-5 years

•5-20% transform to AML

•Treat with JAK2 inhibitors and possibly SCT

Answers to the Qs: 1-20% **2-** AML with recurrent cytogenetic abnormality **3-** thrombocytosis **4-**CML **5-**PMF