Primary myelofibrosis

- It’s a bone marrow fibrosis

- It's type of myeloproliferative disease i.e. neoplastic proliferation of mature cell of myloid linage.

- Its similar to chronic myloid leukemia (CML).

Recall the similarity between them that both are neoplastic proliferation of mature cell but CML occur because of translocation mutation which lead to form philadilphia chromosome

- Increased megakaryopoesis lead to produce high amount of megakaryocyte which release platelet derived growth factor (PDGF)

- PDGF activates fibroblast which synthesizes collagen causing marrow fibrosis.

- At the beginning bone marrow is hypercellular due to granulopoesis and megakarypoiesis with the result that increasing WBC and platelet number.

- Then bone marrow becomes hypocellular due to fibrosis.

- Note that PB at **slide 31** stands for peripheral blood.

- At slide 33 as you see the bone marrow is hypocelluar (at middle of image low of cells)and spindle shaped stroma because of fibrosis .

- At upper right you can notice megakaryocyte which is atypical and large in number while at CML is typical in shape

Myelodisplastic syndrome(MDS)

- Different mutations (high number of mutation) prevent stem cell to continue maturation lead to dysplasia (abnormal shape) and cytopenia(decrease cell count).

- It's common cause of anemia with decrease bone marrow production like megaloblastic anemia.

- Different mutations, but mutations here are more aggresive than myloprolifrative disease.

- Myeloprolifrative disease : mutation occur at gene level (like JAC2 or ABL) but, myelodisplastic syndrome : mutations occur at level of chromosome(all chromosome) and usually deletion mutations so more aggressive mutation and more defective (abnormal) cells.

- Because cell are morphologically abnormal so can't leave the bone marrow to peripheral blood causing peripheral blood cytopenia.

- At slide 35 doctor mean by risk factors which are the smoking, radiation, chemicals …etc.

- At slide 36 recall that - normal number of blast at bone marrow is 5%.

- Classification of MDS according to number of blast fall into three categories (0-6%,6-10%,11-19%)

- If blast more than 20% this disease called acute myloid leukemia (AML).

- Sidieroblstic ring is accumulation of iron at mitochondria which usually found around nucleus, it needs special stain to see it under microscope.

- Hyposegmented nuclei mean just one or two segment. Also, hypolobulated nuclei at megakaryocyte it's one or two lobule.

- Slide 37 the note here is that it's called refractory ; because it's untreated , another thing is RAEB-2 has more probability to progress to acute myloid leukemia(AML).

- Slide 38 : most common case of refractory cytopenia with unilinage dusplasia is erythroid linage (refractory anemia with ring sideroblast) and its best prognosis also, its rarely progress to AML.

Take attention of slide 39.

Acute myloid leukemia

- High number of mutations lead to AML at both levels chromosomal and gne level.

- Remember that myeoprolifrative disease(MPD) occur at gene level and myelodisplastic syndrome(MDS) occur at cheomosomal level.

- (AML affect all ages) while (MPD affects elderly) and (MDS affects middle aged.)

- AML pathogenesis affects both differentiation and proliferation level so cells aren't mature but still proliferate.

- Slide 41 FAB (French American British) classification depends on morphology.

- M1: AML without maturation i.e. blast has the biggest percentage 80% or more.

- M2: AML with maturation but little mature cell with blast (immature cell) the highest percentage of bone marrow cells.
- M3: acute promyelocytic leukemia (here myeloblast has one step maturation to promyelocyte and arrest there), patients with M3 develop DIC commonly bleed and die of bleeding.

- M4:acute myelomonocytic leukemia, occur when high proliferation of monocyte and neutrophils (don't forget even the monocyte and neutrophil number increase here but the percentage of blast should still above of 20% to call AML)

- To more understanding, if I have 20%balst cell and the type is M4 then the rest cells are monocyte and neutrophils.

- M5: acute monocytic leukemia, when high proliferation of monocyte with more than 20%blast.

- M6: acute erthrocytic leukemia, increase number of erythrocytic vell (nucleated RBC) with more than 20% blast

- M7: acute megakaryocytic leukemia, increase number of megakaryocyte with more than 20% blast.

Notice that M6 and M7 are rare cases.

Slide 42

- WHO depend morphology and other criteria like mutations …etc.

- While FAB depend on morphology and it's older but still used.

- WHO most important clinically.

- Inversion 11 is poor prognosis while t(8;21) is good prognosis.

- At 4th point (AML – not otherwise specified) here going back to FAB classification.

Slide 46

- PML (promyelocytic leukemia) gene found at chromosome 15 while RARA (retonic acid receptor alpha)

- DIC which cause hemolytic anemia(microangiopathic hemolytic anemia) producing schstocyte, cellbleeding because of releasing of anti- coagulation factor to remove thrombus, thrompocytopenia.

- So schstocyte, low platelet, increase promylocyte mean M3 (acute promyelocytic leukemia)

Slide 47

- Promyelocte differ from myeloblast. Promyelocyte larger, more greanulated and auer rods commonly found

- Auer rods is accumulation of granules contain enzyme found at cytoplasm of the blast cell at AML.

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عمر بن الخطاب