Myelodysplastic syndrome (MDS) & Myeloproliferative neoplasms

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**Myelodysplastic syndrome (MDS)**

- A multipotent stem cell that can differentiate into any of the myeloid lineage cells (RBCs, granulocytes, megakaryocytes)
  ...become abnormal and proliferate (clonal proliferation), and this abnormal clone will have
    - ineffective
    & - disordered differentiation

- Ineffective hematopoiesis & high risk of transformation to AML
MDS, cont’d

• The marrow: usually is hypercellular or normocellular
• The peripheral blood: one or more cytopenias

• Most cases are idiopathic
  …but some: after chemotherapy with alkylating agents or exposure to
  ionizing radiation therapy
MDS, common genetic/epigenetic abnormalities

• Epigenetic factors
  ... DNA methylation, histone modifications...etc.

• RNA splicing factors
  ... commonly associated with ring sideroblasts

• Transcription factors

• 10%...loss-off function mutations in the tumor suppressor gene TP53
  ...poor outcome

• Also: chromosomal abnormalities, including monosomies 5 and 7, deletions of 5q, 7q, and 20q, and trisomy 8
MDS, morphology

- Abnormal erythroid precursors:
  - megaloblastoid
  - ring sideroblasts

- Abnormal granulocyte precursors:
  - abnormal granules
  - abnormal nuclei

- Abnormal megakaryocytes:
  - small
  - single small nuclei
  - multiple separate nuclei
MDS, clinical notes

• Age: mostly 50-70 years

• Symptoms and signs related to cytopenias
  ...anemia
  ...infections
  ...hemorrhages

• 10-40%: transform to AML
Myeloproliferative neoplasms

...mutated, constitutively activated tyrosine kinases or other acquired aberrations in signaling pathways
...growth factor independence

...tyrosine kinase inhibitors can be used

...neoplastic cells seed secondary lymphoid and hematopoietic organs and cause abnormal hematopoiesis...hepatosplenomegaly
Myeloproliferative neoplasms, cont’d

• **Four major diagnostic entities**
  - Chronic myeloid leukemia (CML)
  - Polycythemia vera
  - Primary myelofibrosis
  - Essential thrombocythemia
Genetics

• CML...characteristic abnormality for CML, the BCR-ABL fusion gene
  ...constitutively active BCR-ABL tyrosine kinase

• Activating mutations in the tyrosine kinase JAK2
  ...in virtually all cases of polycythemia vera and about 50% of
  cases of primary myelofibrosis and essential thrombocythemia

• Others
Myeloproliferative neoplasms, cont’d

• All myeloproliferative neoplasms have variable propensities to transform to:
  
  - a “spent phase” resembling primary myelofibrosis
  or
  - “blast crisis” identical to acute leukemia,

  ...both presumably triggered by the acquisition of other somatic mutations
CML

• Peak incidence: fourth and fifth decades

• Distinguished from other myeloproliferative neoplasms by:
  chimeric BCR-ABL gene: derived from portions of the BCR gene on chromosome 22
  and the ABL gene on chromosome 9

• In about 95% of cases, the BCR-ABL gene is the product of a balanced (9;22)
  translocation that moves ABL from chromosome 9 to a position on chromosome
  22 adjacent to BCR

  ...Although the Ph chromosome is highly characteristic of CML, it also is present in 25% of
  adult B cell–ALLs and a small subset of AMLs
CML, cont’d

- BCR-ABL does not inhibit differentiation, so:
  ...the early disease course is marked by excessive production of relatively normal blood cells, particularly granulocytes and platelets

- Leukocyte count is elevated, often exceeding 100,000 cells/μL

- Circulating cells are predominantly neutrophils, metamyelocytes, and myelocytes...among others (especially basophils)

- The bone marrow is hypercellular

- Extensive extramedullary hematopoiesis...may affect spleen blood supply...splenic infarcts
CML, cont’d

• Onset of CML is insidious

• The initial symptoms usually are nonspecific...easy fatigability, weakness, weight loss

• Sometimes the first symptom is abdominal discomfort caused by splenomegaly

• Distinguish CML from a leukemoid reaction (a dramatic elevation of the granulocyte count in response to infection, stress, chronic inflammation, and certain neoplasms)...testing for the presence of the BCR-ABL fusion gene is important here
CML, cont’d

- Even without treatment, the median survival is 3 years

- Half of CML cases enter an accelerated phase marked by:
  ...increasing anemia and new thrombocytopenia, will transform into a picture resembling acute leukemia (blast crisis)

- In other cases, blast crisis occurs abruptly, without an accelerated phase

- Less commonly, CML progresses to a phase of extensive bone marrow fibrosis resembling primary myelofibrosis

- Tyrosine kinase inhibitors are effective...may become resistant
Polycythemia vera (PV)

• Strongly associated with activating point mutations in the tyrosine kinase JAK2
  ...acts in the signaling pathways downstream of the erythropoietin receptor and other growth factor receptors

• Excessive proliferation of erythroid, granulocytic, and megakaryocytic elements (panmyelosis)
  ...but most clinical signs and symptoms are related to an absolute increase in red cell mass

• Must be distinguished from relative polycythemia, which results from hemoconcentration
PV, cont’d

• Low levels of serum erythropoietin, which is a reflection of the growth factor independent growth of the neoplastic clone...unlike reactive conditions

• Increases in blood volume and viscosity

• The liver is enlarged due to congestion and often contains small foci of extramedullary hematopoiesis

• The spleen usually is slightly enlarged (250 to 300 g) because of vascular congestion

• Thromboses and infarctions are common, particularly in the heart, spleen, and kidneys
PV, cont’d

• Platelets produced from the neoplastic clone often are dysfunctional, a derangement that contributes to the elevated risk of thrombosis and bleeding

• As in CML, the peripheral blood often shows basophilia

• The bone marrow is hypercellular owing to increased numbers of erythroid, myeloid, and megakaryocytic forms
PV, cont’d

• Appears insidiously, usually in late middle age
• Plethoric and often somewhat cyanotic facies
• Histamine released from the neoplastic basophils
  ...pruritus
  ...increased incidence of peptic ulceration
• Thrombotic and hemorrhagic tendencies
• Hypertension
• Headache, dizziness, gastrointestinal symptoms, hematemesis, and melena are common
• Because of the high rate of cell turnover, symptomatic gout is seen in 5% to 10% of cases
PV, cont’d

• Hematocrit is often 60% or greater
• The granulocyte count can be as high as 50,000 cells/μL
• The platelet count is often more than 400,000/μL
• Basophilia is common
• Platelets are functionally abnormal in most cases, and giant platelets and megakaryocyte fragments are often seen in the blood
• 30% of patients develop thrombotic complications, usually affecting the brain or heart
• Hepatic vein thrombosis giving rise to Budd-Chiari syndrome is an uncommon but grave complication
• Epistaxis and bleeding from gums
• In those receiving no treatment, death occurs from vascular complications within months
  ...however, the median survival is increased to about 10 years by lowering the red cell count to near normal through repeated phlebotomy
• Unfortunately, prolonged survival has shown a propensity for polycythemia vera to evolve to a “spent phase”
  ...After an average interval of 10 years, 15% to 20% of cases undergo such a transformation
PV, cont’d

• Inhibitors that target JAK2 have been approved for treatment

• Transformation to a “blast crisis” identical to AML also occurs, but much less frequently than in CML
Primary myelofibrosis

• The hallmark of primary myelofibrosis is:
  obliterative marrow fibrosis, which reduces bone marrow
  hematopoiesis and leads to:
    ...cytopenias and extensive extramedullary hematopoiesis

• JAK-STAT signaling seems to be the underlying driver in almost all cases

• Transformation to AML occurs in 5% to 20% of cases

• JAK2 inhibitors are effective
Primary myelofibrosis

• In peripheral blood smear:
  abnormal red cells that often exhibit bizarre shapes (poikilocytes, teardrop cells), and nucleated erythroid precursors are commonly seen along
  +
  immature white cells (myelocytes and metamyelocytes)

= leukoerythroblastosis

• Abnormally large platelets often are present as well
Primary myelofibrosis, clinical notes

• Usually older than 60 years

• Progressive anemia + splenomegaly

• Also abnormal platelets and risk of bleeding & thrombosis

• 4-5 years but more difficult to treat than CML and PV

• JAK2 inhibitors decrease the symptoms
Thank You