Hemolytic anemia –part 4 // Polycythemia

Hemolytic anemia –part 4 includes: Glucose -6-Phosphate-Dehydrogenase Deficiency & Paroxysmal Nocturnal Hemoglobinuria

First: Glucose -6-Phosphate-Dehydrogenase Deficiency:

Abnormalities (mutations) in G6PD gene that affect the enzymes responsible for the synthesis of GSH which inactivates both exogenous and endogenous oxidants. These abnormalities result in leaving red cell prone to oxidative injuries and lead to hemolytic anemia.

Note: G6PD gene is located on the X chromosome

1. **Mechanism of G6PD deficiency anemia**
   a. G6PD deficiency produces no symptoms until the patient is exposed to an environmental factor that produces oxidants. Environmental factors include:
      - Infections: because it induces phagocytes to generate oxidants as part of the normal host response. → more common
      - Drugs: antimalarials (primaquine) /sulfonamide/ nitrofurantion /phenacetin /aspirin (in large doses) /vitamin K derivatives.

      So oxidants produced are free to attack other red cell components including globin chains which have sulfhydryl group that are prone to oxidation--→ oxidized hemoglobin denatures and precipitate forming intracellular inclusions called Heinz bodies --→ Heinz bodies:

      - Either: damage the cell membrane and cause (intravascular hemolysis)
      - Or: other less severely damaged cells lose their deformability and suffer further injury when splenic phagocytes try to pluck out the Heinz bodies creating so called bite cells ,which will be destroyed in the spleen (extravascular hemolysis)

      Note: since G6PD is X linked, males are affected more (all red cells are G6PD deficient) than heterozygous females (which will have 2 populations of red cell: one with normal amount of G6PD and the other one with deficient G6PD).so heterozygous females are usually unaffected.

2. **G6PD variants**: mutations of G6Pd are so many creating what is called G6PD variants which may be pathogenic or nonpathogenic , pathogenic variants include:
   a. G6PD A- : has a normal enzymatic activity but a decreased half life .because red cells don't synthesize proteins ,older red cells are the cells deficient in G6PD which makes them more sensitive to oxidants.
      This variant is common among black males (remember G6PD on X chromosome) in U.S.A

b. G6PD Mediterranean: in the middle east

3. **Symptoms and manifestations**:
   a. classified according to the triggering agent (drugs / infections)
      drug induced hemolysis is acute , of variable severity ,and develops after 2-3 days after exposure.
   b. Classified according to the variant:
      A-is less severe than the Mediterranean variant because in A- only old red cell are affected which will be compensated by erythropoiesis in the bone marrow.

Second: Paroxysmal Nocturnal Hemoglobinuria (PNH):

It is the only hemolytic anemia that results from an acquired somatic mutation in myeloid stem cells.

1. **Cause**: acquired mutations in gene PIGA (X-linked gene) which is required for the synthesis of membrane anchor (PIG=Phosphatidyl Inositol Glycan) which anchors proteins on the cell surface. So without PIG surface proteins cannot be anchored. The affected surface proteins include proteins that inhibit the alternative pathway of the complement system .as a result, PIG deficient red cells and leukocytes are sensitive to complement mediated lysis.
   Note:
   - PIGA gene mutation must occur in an early myeloid progenitor with self renewal capacity (myeloid stem cell) because these mutations affect both red cells & leukocytes.

   Although mutations in PIGA gene would normally cause PNH, some normal individuals have some bone marrow cells with PIGA gene mutations. It is believed that PNH occurs when PIGA mutated cells have a survival advantage, such as: aplastic anemia (primary bone marrow failure) which is caused by immune mediated destruction of marrow stem cells.
   The reason of deficient PIGA advantage is : PIGA deficient stem cells somehow escape the immune attack and eventually replace the normal marrow elements.
   Notes:
   - PIG deficient Leukocytes are less affected than PIG deficient RBCs
   - The reason of naming this anemia is :
     First: its attacks comes in cycles (paroxysmal)
     Second: its attacks occur at night (nocturnal) because complement fixation is enhanced at night during sleep due to a decrease in blood Ph as a result of high CO_2 concentration.

2. **Symptoms and manifestations:**
   a. Patients mostly present with mild anemia due to chronic mild hemolysis
   b. Venous thrombosis : a fetal complication caused by a product of the complement activation which is MAC (membrane attack complex) which induces thrombosis

3. **Treatment:**
   Targeted therapy with an antibody that inhibit MAC (C5b+C6+C7+C8+C9) is effective in treating hemolysis and thrombosis
   But!!!
   This treatment places patients at high risk for Neisseria infections including meningococcal sepsis.

Polycythemia (OR erythrocytosis):

An increase in red cells per unit volume of peripheral blood usually associated with increase in hemoglobin concentration.

Polycythemia is classified to :

1. **Relative** : results from dehydration which reduces plasma volume and thus there is an apparent (not real)erythrocytosis
   Dehydration is caused in several situations such as:
   (Water deprivation /prolonged vomiting/ diarrhea/ excessive diuretics).

2. **Absolute**: increase in total red cell mass .classified according to inducer of erythrocytosis to:
   a. **Primary** (self induced): results from autonomous proliferation of erythroid progenitors. Cause is:
      Abnormal proliferation of myeloid stem cell (Polycythemia Vera) caused by inherited activating mutations in the erythropoietin receptor, in this case the levels of erythropoietin are mostly low but could be normal.
      Note: Polycythemia Vera will be discussed below.
   b. **Secondary:** results from elevated levels of erythropoietin which induces excessive proliferation of erythroid progenitor cells. Causes are:
      I. Adaptive (high erythropoietin levels in response to): lung disease/ high altitude living / cyanotic heart disease.
      II. Paraneoplastic (erythropoietin –secreting tumors): renal cell carcinoma /hepatomacellular carcinoma /cerebellar hemangioblastoma)
      III. Surreptitious (used illegally) : endurance athletes.

Polycythemia Vera: clonal, neoplastic myeloproliferative disorder.

1. **Characterized by:**
   a. an 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.
   b. Low levels of serum erythropoietin unlike reactive (secondary absolute) of Polycythemia. Low levels of erythropoietin reflect growth factor independent growth of neoplasia.

2. **Cause:**
   Activating mutations in JAK2, tyrosine kinase (a signal transducer) downstream growth factor receptors. The most common JAK2 mutation is a valine to phenylalanine substitution at residue 617.

3. **Signs and clinical manifestations/ morphology:**
   a. General common signs: insidious, late middle aged patients having some degree of cyanosis, headache, dizziness, gastrointestinal symptoms, hematemesis, and melana.
   b. Anatomic changes stem from increases in blood volume and viscosity.
      I. Plethoric (filled with blood) congestion of tissues
      II. Liver enlargement with small foci of extramedullary hematopoiesis.
      III. Spleen is slightly enlarged due to vascular congestion
   c. Thromboses and infarctions as a result of increased viscosity, vascular stasis, and dysfunctional platelets. Mostly affects the: heart / spleen / kidney/ brain /liver.
   In some cases hepatic vain thromboses develops which gives rise to Budd – Chiari syndrome (fatal)
   d. Hypertension
   e. Hemorrhages: as a result of excessive distention of blood vessels and dysfunctional platelets. Mostly affects the gastrointestinal tract/ brain / oropharynx.
      Hemorrhages may be:
      I. Minor (common): e.g. epistaxis and bleeding from the gums.
      II. Major (life threatening).
   f. Definitive diagnostic signs:
      I. Red cell count is high (6-10 million / microleter)
      II. Hematocrit is 60% or greater
      III. Granulocyte count is high (50000 cells /microleter)
      IV. Basophilia is common .
      Note: histamine released from the neoplastic basophiles may contribute to pruitus and peptic ulcers.
      V. Dysfunctional platelets and giant platelets and megakaryocytes fragments are seen in blood.

VI. Hypercellular bone marrow (increased erythroid ,myeloid ,megakaryocytes numbers)

VII. 10% of patients have some degree of marrow fibrosis.

4. Treatment:

a. No treatment is fatal within months as a result from vascular complications.

b. Repeated phlebotomy increases survival rate.

c. JAK2 inhibitors are in clinical trials at present

5. Complications:

- Overtime some patients who survive Polycythemia Vera complications (thromboses , hemorrhage, infarctions, ….etc) develop a spent phase resembling primary myelofibrosis where the bone marrow is largely replaced by fibroblasts and collagen. As a result of extensive fibrosis hematopoiesis shifts to the spleen which enlarges markedly
- transformation to a blast crisis identical to AML (acute myelogenous leukemia) occurs but much less frequently than in CML(chronic myelogenous leukemia)

Note: blast crisis is a sudden, severe change in the course of chronic myelogenous leukemia, characterized by an increased number of blasts that mimics the number of blasts in acute myelogenous leukemia.

Done By: Fekra….Good luck!!!