Hematology

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Anemia's (Cont'd)

In today's lecture we're going to continue our talk about the different types of anemia. So let's begin with:

I. Hemolytic anemia

1. Autoimmune Hemolytic anemias:

Etiology: it's secondary to synthesis of abnormal immunoglobulins that target normal cell membrane proteins on the RBCs.

Diagnosis: Is done by Coomb's test. So what is meant by Coomb's test?

Normally there are antibodies that bind to the surface of RBCs. So in this test we give a serum that has antibodies against the human, antibodies that target the antibodies on the RBCs surface, if he has the disease, they will combine and cause the RBCs to come close to each other causing what's known as "agglutination" and they can't separate and as a result there will be turbidity.

From slide > the patient's blood is mixed with serum containing antibodies that are specific for human immunoglobulin. If the auto-antibody is present, agglutination of RBC occurs.

Now the first pathology to be discussed regarding autoimmune hemolytic anemia is:

i. The Warm Type.

Nomenclature: named so because it occurs in *the body's core* i.e., the trunk and the central of the body where the temperature is normally 37 degrees.

Note: Auto-antibodies of interest are both *IgG* which is by far the most common one and *IgA.*

Etiology:

- 50% of the cases are idiopathic meaning that there isn't any discovered reason yet, the patient is having the disease without an apparent or obvious reason.
- The remaining 50% is usually due to drugs which are *administered intravenously with large doses and the most common ones are antibiotics like cephalosporin and penicillin.*

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so a clinical scenario might be as following: A patient comes to your clinic with severe sepsis or infection and is being treated with a large IV dose so after 1-2 weeks which is the normal period for synthesis and he is diagnosed with warm type hemolytic anemia. Other drugs including anti-malarial drugs "previously mentioned in G6PD crisis" and finally Methyl-Dopa which is an antihypertensive drug commonly prescribed for pregnant women. So all in all these drugs cause hemolytic anemia but the mechanism by which each of these drugs causes it is different, for example:

-Penicillin drugs can attache themselves to the cell's surface so the body fights them as if they are foreign bodies through antibodies attached to the cell surface.

- Methyl-Dopa does not adhere to the cell surface and its mechanism is not known yet.

Pathophysiology: Now what occurs next is that the RBCs are coated with anti-bodies and then they reach the spleen, normally the immunoglobulin IgG has an fc fragment which attaches to the spleen's macrophages "Histiocytes", then these RBCs are identified by those histiocytes which catch them through the fc fragment and then part of the cell membrane is lost by these hisiocytes through pinching the part of the membrane containing the immunoglobulin leading to a morphology similar to that we see in case of hereditary spehrocytosis so we end up with spehrocytes. Spehrocytes move in the circulation, reaching the spleen again and is destroyed there and finally can be recognized on a blood film. It is also associated with extra-vascular hemolysis so these patients suffer from jaundice and splenomegaly.

ii. The Cold Type.

Nomenclature: named so because it affects *the peripheral circulation* commonly in organs like: nose, fingers, toes and *heels* because temperature in these organs is much lower than the body's core.

Note: Auto-Antibody of interest here is *IgM* which is a large pentamer that can catch 5 targets.

Now we have two clinical settings for this disease:

(1) *Acute:* it can appear suddenly "acutely" commonly following an infection and the most well-known type is mycoplsama pneumonia which causes pneumonia and also know to cause cold type

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autoimmune hemolytic anemia and the second cause is the influenza virus which causes a self-limited disease, a patient comes to your clinic with pneumonia and is treated and he achieved full recovery then after 1-2 weeks he comes back with immune cell anemia but it is self-limited so it goes by its own.

(2) *Chronic* which is persistent and severe and most commonly seen in cases of lymphomas they can be functional and secrete huge amounts of immunoglobulins including IgM, so they cause hemolytic anemia and in this case it's lymphoma "cancer" and persistent you can't cure the anemia without curing the lymphoma.

Pathophysiology: Now what occurs is that usually IgM is active at the colder temperatures i.e. in the periphery it is attached to the cell surface of the RBCs and once it attaches it attracts the complement system "an activator of the immunoglobulins" so it brings the complement system to adhere to the cell's surface to start their function which is cell lysis. Now, IgM, when the RBCs return to the core where the temperature increases, IgM detaches from the RBCs leaving the complement system there.

In a nut shell:

A. Adherence of the IgM to the cell's surface
B. Attracting part of the complement system "it's of short duration so we don't have a complete activation of the complement system so we get a subclinical one i.e. part of the complement is attached they don't have enough time to complete their work.
C. Then when the RBCs return back to the high temperatures, IgM leaves RBCs and the complement system stays there.
D. They reach the spleen, which can sense the complement system and take them out causing a spherocyte to form at the end, spehrocyte s return to the spleen in a second circulation and then are destroyed, so these patients have extra-vascular hemolysis.

Additional lab findings: as we know IgM is a large molecule it can attache to 5 cells together so on a blood film we can see the RBCs agglutinated together i.e. clumped together in large amounts.

2. Trauma to the RBCs

a. *Physical trauma* directed to RBCS, destroying them and it occurs intra-vascular not in the spleen. Examples include: vigorous strenuous exercises, i.e. any physical exercise which is very strong that can reach what's inside blood and causes destruction. Commonly seen in sports like boxing, marching like in marathon running and military.

b. *Prosthetic valves*, normal cardiac valves can be replaced with metallic ones and theses are considered as foreign bodies which can destroy the RBCs while blood is flowing to the heart.

c. *Microangiopathic diseases* they are a group of diseases discussed later on, but in general we have widespread thrombi in the capillaries everywhere in the body. Thrombi cause physical damage to the RBCs when they pass through them.

Note: The common thing between them is that we see broken RBCs referred to as *schictocytes* "schicto (torn/ broken) cytes (cells)" they appear as fragmented cells.

3. hypersplenisim

It is relevant to an increased function of the spleen and it's a special type of splenomegaly while splenomegaly is an increase in size. One more thing is that hypersplenism is not related to haemolytic disease (not secondary to haemolytic anemia) as it can be associated with *other diseases like Rheumatoid Arthritis.*

Pathophysiology: What occurs is that the spleen increases in size with a marked increase in function causing destruction not only to RBCs but also to WBCs and platelets so as a consequence patients would have pancytopenia in the peripheral blood in addition to anemia, leucopoenia, thrombocytopenia and ultimately a very large spleen.

Note (1): Splenomegaly is a large spleen while hypersplenisim is a large and hyper-active spleen

Note (2): *Felty's syndrome is when the above clinical setting occurs along with rheumatoid arthritis.*

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4. Sickle cell anemia

Best known for sequestration syndrome or crisis where the spleen becomes massively enlarged and thus engulfing the entire blood. In this setting the anemia is normochromic normocytic because there is no pathology in the RBCs themselves.

And now we're done with the haemolytic anemia ✌

II. 2nd category Decreased bone marrow production

1) Iron Deficiency anemia.

Is the most common type of anemia and its most common cause is that there is no enough iron in the diet i.e. nutritional cause.

Normally iron is present in flesh "red meat" and in vegetables but in human beings they don't have the capability to absorb iron from vegetables. The most abundant source for it is the red meat but red meat is not available for everyone.

a. The infants can't eat meat so they suffer from iron deficiency anemia as well as growing children have increased demands so they need more iron.
b. Old people have difficulty in chewing meat so they also suffer from iron deficiency.
c. Pregnant women they need more iron than normal women and maybe they don't have access to enough red meat.
d. GI diseases and here the absorption of iron is decreased as we see in many GI diseases like IBD (inflammatory bowel disease) and Celiac disease leading to iron deficiency anemia.
e. Blood loss "chronic blood loss" would also cause iron deficiency anemia.

Prevalence: Iron deficiency anemia is the most common type of anemia as previously mentioned worldwide specifically in developing countries like in our region while in the west they have a lower incident.

Pathogenesis:

- Iron is deficient so no enough Heme synthesis and ultimately no enough Hb synthesis so the RBCs will look small and pale i.e. microcytic hypochromic anemia
- Although erythropoietin is increased in patients having anemia and also hypoxia. But in iron deficiency there are no enough stores in the body it will block the bone marrow and become not sensitive to erythropoietin even if it is present in high amounts and the exact mechanism is not known yet. So no enough production of RBCs although erythropoietin is high in contrast to what happens in thalassemia they have ineffective erythropoiesis i.e. there is erythrocytosis but still anemia is present while in iron deficiency there is high erythropoietin but RBCs are low because bone marrow is not responding, so normoblasts are small in size with short life because of no response to erythropoietin.

Morphology: Another feature for RBCs in iron deficiency, iron deficiency itself causes changes in the environment inside the RBCs so the cell membrane would become more rigid than normal so piokilocytosis i.e. RBCs with different shapes most commonly seen in iron deficiency anemia. As a result the rigid membrane causes a minor degree of hemolysis but not classified under haemolytic anemia because it is not a major mechanism or issue like the previous mentioned ones it's just an indication when you do the Lactate Dehydrogenase test it would be slightly increased but patients would not have splenomegaly no jaundice and no other features.

Note: *Iron deficiency is a major cause of thrompocytosis* most patients come with hypochromic microcytic anemia and there is an increase in platelet count with no full explanation to that but some theories would suggest that erythropoietin would cross react with the megakaryocytes and through receptors it causes activation and synthesis but that does not explain how it occurs in other diseases like thalassemia or haemolytic anemia.

Lab findings: On the Blood film RBCs are having a *very pale central part and the central pallor is more than one third and smaller size with different shapes not all of them are round we have elliptical, elongated ones and few target cells* which are seen in thalassemia and sickle cell

anemia, and they *indicate abnormal hemoglobinization* and the same here in iron deficiency there is no hemoglobin so they appear but it's more common or obvious in thalassemia.

Systemic symptoms associated with iron deficiency:

Most of them have no explanation i.e. why these symptoms appear. Iron is most commonly found in the body in the hematopoietic system and in muscles as myoglobin but when there is deficiency symptoms appear in the entire body, epithelial cells, neurons of the CNS and finally an entire cellular defect in the body related to *cooperation* cells which are always active besides hematopoietic ones we have epithelial cells of the skin that produce hair and nails are affected so:

- Patients with iron deficiency have hair loss commonly in addition to thin and fragile nails which with physical movement and traumas they become abnormally round they are not very rigid so patients have *spoon like fingers*.

- Epithelial injury in the GI system like in case of glossitis inflammation of the tongue and stomatitis inflammation of the lips in addition to abnormal muscle movement in the GI system i.e. abnormal peristalsis and the most common organ affected is the esophagus with abnormal peristalsis in addition to the epithelium injury so the epithelium is weak these patients have a weak mucosa and it can go out i.e. bulging out of the normal place so the esophageal lumen will be narrow because the mucosa is going outside and this is clinically referred to as *"Web"* resembling spider webs and it can cause symptoms like dysphegea so they can't swallow normally and you can diagnose it through the endoscope by using barium which is radio-opaque the patient drinks it and then we do an x-ray and you see the fluid going down until there is narrowing in the esophageal junction so this is the web associated with iron deficiency.

- They also have *blue sclera*, the sclera is very thin so it shows the veins behind it and the eye appears bluish.

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- *Neurologic diseases along with cognitive dysfunctions* which are most commonly seen in children and considered as a bad thing for school aged children and if untreated which is common when the awareness is low and along with their bad habits they will have impairment in the neurologic and cognitive functions in the higher functions of the brain.
- *Pica* means eating and chewing unusual stuff with no known cause, things like ice, paints of the walls while others eat soil.
- A new symptom associated with iron deficiency is a one called *stressed leg syndrome*.

2) Megaloblastic anemia.

-*Is a deficiency in vitamin b.12 or folate or both of them.*

-Vit.b12 is exclusively found in animal products like in red meat, milk, pigs, but not in vegetables, so vegetarian people will have this deficiency.

-Pernicious anemia and GI disease both lead to the same thing, that is, patients don't absorb vitamin b12 and is usually multifactorial, meaning they'll have deficiency in iron, vitamin b12 and other things...

-Now pernicious anemia is an autoimmune disease in the stomach that causes destruction of the parietal cells, which are responsible for the production of the intrinsic factor that adheres to vitamin b12 forming a complex that then goes to the circulation.

So, no parietal cells---->no intrinsic factor---->vitamin b12 that's found in food will not be absorbed.

Note: Some people have an inherited loss of these intrinsic factors, and it is obvious here that they will also develop pernicious anemia.

-Folate: it is a deficiency which can be caused by nutritional reasons when the individual is not eating enough green leaves and vegetables where folate is abundant in, but the most common cause of folate deficiency is the increased demand of it like in pregnant women.

Remember that Folate has a high turnover, way higher than that of vitamin b12 and iron! for example, vitamin b12 stays around one year; meaning that if

we cut off vitamin b12 supply for one year, it takes one whole year for its' stored amounts to be depleted. That's why in the first pregnant visit, I give her vitamin b12 supplement because the baby needs folate (b12 is needed for folate)

-Second cause is: *Drugs*

We have so many drugs that inhibit the absorption or utilization -at the cellular level- of folate and vit.B12, like*: (anti-epilepsy drugs, OCP oral contraceptive pills, methotrexate used in chemotherapy)*

The doctor said how methotrexate inhibits DNA replication of folate at the cellular level.

-Vitamin b12 deficiency: By itself causes functional folate deficiency- because they need each other to work.

-Dialysis, in chronic renal failure: they lose part of the folic acid.

Pathogenesis:

-Now, both vitamin b12 and folate are essential for the synthesis of thymidine which is a nucleic acid on the DNA molecule, so, if you don't have thymidine, the cells will have abnormal maturation and replication, meaning that they will take a longer time to replicate, and that's what we call delayed hematopoietic cells maturation.

Morphology:

-They appear as large normoblasts(macroovalocytes), why? *Because they take a longer time, the nucleus takes a longer time to work and mature while the cytoplasm is growing normally. So, cytoplasm is large and nucleus hasn't matured yet, that's why we call it (Megaloblastic), Mega: large, blastic: immature, not enough DNA replication, pale nucleus.*

-Same thing happens with the *neutrophils*. Usually neutrophils are segmented but here WBCs cannot mature like normal ones, they take a longer time! so, the nucleus will have a chance to divide more and to be segmented more, so in this diseases we have extra segments, normally, it is up to 5, *in vit. B12 deficiency, they become hyper segmented, 6 or more! And also, they have large cells. Most famous ones are giant cells.*

For the megakaryocytes, also they appear larger and more lobulated (the nucleus has more lobes). DNA, as we said, is not normally functioning, so these cells die -prematurely- inside the bone marrow, so it's like hemolysis, but not like hemolytic anemia, here it's in the bone marrow, and so they don't have jaundice or splenomegaly.

Note (1): B12 is important for myelin synthesis in the CNS.

No vit.B12--->No enough myelin--->nerves will be injure--->a patient will have neurologic symptoms--->(neurologic symptoms begin in the spinal cord with sensation, sensation is defected in these patient, or any position sense, other sensory signals will be disturbed, so *they'll suffer from numbness in their hands even pain, if not treated, symptoms will start to appear in the higher functional levels (in the motor) and higher cognitive eruptions of the brain), so they'll suffer from dementia and loss of memory.*

Note (2): vit.B12 causes neurological symptoms, while folate deficiency does not.

Morphology: -Megaloblastic anemia, in a blood film and as we see, they're large cells and slightly oval (macroovalocytes), and even the central pallor, sometimes disappears! For neutrophils, they are hyper-segmented (6 or more).

-In the bone marrow, on the left they are normal (normoblasts) and on the right (Megaloblastic anemia) they are larger in size and the nucleus is more pale that's why we called it megaloblastic.

3) Anemia of chronic Diseases

-Any chronic diseases especially chronic infections can cause anemia (like Tuberculosis), cancer, and rheumatologic diseases. This is most common for hospitalized patients.

Pathogenesis:

-we have chronic inflammation---> high levels of IL-6--->activated Hepcidin--->blocks transfer of iron from their stores to the normoblasts---> even if you have large amounts of iron, the cells cannot utilize it--->relative deficiency of iron.

There's another feature also, now we know that *iron is present in Macrophages, so if you populate a large number of macrophages like in case of chronic inflammation, also the iron will be shifted to macrophages instead of normoblasts.*

Morphology:

-*Initially they have normochromic normocytic anemia, but with time, it becomes like iron deficiency anemia (hypochromic microcytic).* How can we differentiate? We check *Hemosiderin* in the bone marrow, in IDA its low but in this disease it's very high because it's not utilized.

Also, serum *ferritin is high in contrast to iron deficiency which has low amounts.*

Treatment:

Is to treat the underlying cause meaning that you cannot treat anemia if you don't treat the real reason behind it.

4) Aplastic Anemia

-It's a total clone marrow failure, where it cannot produce ANY cell, and most commonly *it's idiopathic*, so they manifest without any previous disease, while the rest might have *autoimmune disease somewhere like thyroid, pernicious anemia, and one of them in the bone marrow they have abnormal cells that destroy the normal cells. Also, Drugs like (chloramphenicol) which is an antibiotic that causes aplastic anemia. And viral hepatitis.*

Prevalence: This disease is common in children and young adults.

-It is *acquired in most cases but sometimes it's congenital we call it Fanconi anemia; aplastic anemia that is congenital*, the baby is born with defective stem cells that cannot produce enough bone marrow cells. Sometimes, we have aplasia only in red cell (erythroid) line, so if you take biopsy from the bone marrow, you'll see myeloid and megakaryocytes but you don't see normoblasts, this is called pure red cell aplasia.

Note: *Congenital is different from inherited. Congenital--->begins during uterine life. Inherited--->you transmit from one to the second*

Pathogenesis:

For the acquired case, the most acceptable theory, have these apparent T-cells (abnormally functioning) that destroystem bone cells. *Anemia would be normochromic normocytic anemia with Pancytopenia.*

Diagnosis: *We conduct a bone marrow biopsy and we notice the predominance of fat over the hematopoietic cells.* (Normally, bone marrow consists of hematopoietic cells and fat, not hematopoietic cells, so you'll see more fat)

5) Myelopthisic anemia

-Physical destruction of the bone marrow by any mechanism, most commonly cancer. Cancer causes replacement and destruction of the hematopoietic cells. So it is infiltrative disease.

Causes: Malignancy (especially those of hematopoietic tumors like Leukemia. Also myeloma, plasma cell lymphoma, they proliferate and destroy the normal hematopoietic cells. Also, metastasis from far.

Granuloma: a granuloma is a large amount of histiocytes that transform into multi-nucleated giant cells and they form masses so they destroy the bone marrow.

Storage diseases *are enzymatic deficiencies and are inherited; the body will accumulate certain materials like glycogen, lipids, and lysosomes. So the bone marrow will be full of macrophages that have this disease.*

In all of them, *we'll have pancytopenia, meaning that it's not selective for RBCs* (the whole bone marrow is failing so we'll develop normochromic normocytic anemia with Pancytopenia).

6) Hypothyroidism

-Thyroxin is essential for cell metabolism anywhere in the body, if we have no Thyroxin, RBCs and hematopoietic cells will not mature normally, so they *will have microcytic anemia.*

7) Chronic renal failure

-In early stages, there's no synthesis of erythropoietin, this is THE ONLY ANEMIA THAT HAS LOW ERYTHROPOIETIN.

In early stages, no erythropoietin--->no production of the RBCs from the bone marrow--->and morphologically, they appear normochromic normocytic.

Now when the disease advances, we reach "uremia" which is basically accumulation of large amounts of toxic uric acid. Now this uric acid will change RBCs' morphology so we'll have circumferential spikes, we call them *ecchinocytes.*

8) Chronic liver disease

-Multifactorial.

Liver is a major organ; it synthesizes the clotting factor---no liver, no clotting factor, they bleed, anemia of blood loss--- also, vitamin b12 is stored in the liver---no liver, no vit.b12 is stored, deficiency in vitamin b12, megaloblastic anemia---also, lipid synthesis so if it's defective, the RBCs will be abnormal, so it is multifactorial meaning that patients with liver disease will have anemia but can be any type!

Regarding the defective lipid synthesis-->RBCs will have longer projections we call it acanthocytes.

9) Myelodysplastic syndrome

-It is *acquired, neoplastic, it's a bone marrow failure but neoplastic!* Different from aplastic anemia. Stem cells have many mutations that disturb the normal maturation of cells (even less mature than megaloblastic, and cannot even leave the bone marrow, so the patients will have pancytopenia, but the bone marrow is full of cells, unlike aplastic anemia!)

- *Can potentially progress into leukemia*

-Can be normochrmoic normocytic or macrocytic anemia (because we have a stem cell disease, remember that stem cell diseases commonly give rise to large RBCs).

Cheers ✌

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