Hemepath Case 13: 4-Month-Old Girl

HISTORY

A 4-month-old baby girl of Mediterranean descent is brought in by her father as she appears pale and has not been gaining weight. The child also has a “lump” in her upper left abdomen.

On physical examination, the girl is noted to be lethargic. Her skin is pale and her sclera has a tinge of yellow. The zygomatic bones are disproportionably larger than the rest of her facial bones. The spleen is palpable 5 cm below the left costal margin.

CBC

Hgb (g/L)	Low
MCV	Low
RBC count	High
Reticulocyte Count	High
WBC	N
Plt	N

OTHER LABORATORY FINDINGS

HbA_2	Increased
HbF	Increased

DESCRIPTION OF SLIDE

Peripheral Blood Smear

There is clear evidence of severe anemia with marked erythroblastosis. Some erythroblasts contain Fessas bodies (precipitated α-globin; see arrows). Also, note the severe targeting, as well as the presence of Howell-Jolly bodies (see circles). There is a mild RBC dysplasia, reflecting stress erythropoiesis (see rectangles).

*** To see the slide annotations in Imagescope, click on VIEW, then ANNOTATIONS, and then on the "eye" icon adjacent to the word "Layers". In the “Layer Attributes” box, a brief description of the annotations is provided. You may also click on individual layer region (e.g. region 1) in the “Layer Regions” box to locate each annotation – this is especially helpful in identifying annotations when the slide is not zoomed in. ***

MORPHOLOGICAL DIAGNOSIS

Thalassemia major. Results from other laboratory testing (high HbA_2, high HbF) permit a diagnosis of Beta thalassemia major.

DISCUSSION

A molecule of normal adult hemoglobin (Hgb A) consists of two α globin chains and two β globin chains, each bound to a heme moiety. It is represented as $\alpha_2\beta_2$. Thalassemia is a group of disorders characterized by deficient synthesis of one or more of these globin chains. The type of thalassemia is determined by which chain is deficient: for example, in β-thalassemia the β chain is deficient. In general, the deficient chains are qualitatively normal despite their quantitative deficiency (although there are exceptions to this rule). Patients with thalassemia usually have a microcytic anemia, whose severity depends on the extent of globin chain deficiency.

Interestingly, anemia in thalassemia does not arise directly as a consequence of globin chain deficiency (unlike iron deficiency, in which anemia arises because heme synthesis is impaired, leading directly to a deficit of hemoglobin in the developing erythroid precursors in the bone marrow). Patients with thalassemia have *unbalanced globin chain synthesis*: in β-thalassemia there is a relative excess of α chains, and in α-thalassemia there is a relative excess of β chains. These excess chains are toxic to the developing red cell. In β-thalassemia, for example, the excess α chains have insufficient β chains with which to partner, so they form α tetramers which are chemically unstable. These unstable α globin tetramers precipitate within the erythroblast, causing membrane injury. The injured red cell may lyse within the bone marrow (intramedullary hemolysis) or may be more prone to early destruction in the spleen. In this way, thalassemia is properly considered a type of hemolytic anemia.

In response to this RBC destruction, the bone marrow compensates by increasing the amount of erythropoiesis, leading to marrow erythroid hyperplasia. In severe cases, the erythroid hyperplasia is so extreme that the marrow space itself is expanded. This can force apart the cortices of the facial and skull bones, leading to deformed zygomatic bones and a deformed calvarium (which can be seen as the classic “hair on end” appearance in a lateral skull X-ray). Splenomegaly arises for two separate reasons: there is excessive clearance of RBCs, expanding the splenic sinuses, and there may in severe cases be extramedullary hematopoiesis.

Genotypically, β-thalassemia is classified on the basis of what type of mutations affect the two β genes carried by the patient (on chromosome 11). β-thalassemia mutations are either β^0 mutations (in which no β globin is synthesized from that chromosome) or β^+ mutations (in which a reduced quantity of β chain is synthesized). A patient who inherits a single β^0 mutation from one parent and a normal β gene from the other parent would be designated $\beta\beta^0$; a patient who inherits two β^+ mutations would be $\beta^+\beta^+$; and so on.

Clinically, β-thalassemia is divided into three categories: β-thalassemia minor, intermedia, and major. This clinical distinction is made primarily by reference to the required frequency of blood transfusion in the patient.

Patients with β-thalassemia *minor* have a microcytic anemia but do not generally require blood transfusion outside of exceptional circumstances (e.g. infection with Parvovirus leading to transient erythroid aplasia). Genotypically, these patients would most commonly be $\beta\beta^0$ or $\beta\beta^+$.

Patients with β-thalassemia *major* are transfusion dependent for their entire lives, i.e. they require regular RBC transfusion to survive. They have severe microcytic anemia. Genotypically, these patients would likely be $\beta^0\beta^0$ or $\beta^0\beta^+$, or possibly $\beta^+\beta^+$ if both "+" mutations led to severe reductions in β chain synthesis.

Patients with β-thalassemia *intermedia* are hematologically and genotypically similar to thal major patients (i.e. severe microcytic anemia, commonly $\beta^0\beta^0$, $\beta^+\beta^+$, or $\beta^0\beta^+$), but only require occasional RBC transfusion.

In patients with thal intermedia and major, there is such a severe deficiency of Hemoglobin A that the red cells instead contain mostly Hemoglobin F (fetal hemoglobin, $\alpha_2\gamma_2$).