

**Please read this section first**

The HPCSA and the Med Tech Society have confirmed that this clinical case study, plus your routine review of your EQA reports from Thistle QA, should be documented as a "Journal Club" activity. This means that you must record those attending for CEU purposes. Thistle will not issue a certificate to cover these activities, nor send out "correct" answers to the CEU questions at the end of this case study.

**The Thistle QA CEU No is: MT- 18/059**

Each attendee should claim ONE CEU points for completing this Quality Control Journal Club exercise, and retain a copy of the relevant Thistle QA Participation Certificate as proof of registration on a Thistle QA EQA.

**DIFFERENTIAL SLIDES LEGEND**  
**CYCLE 52 SLIDE 3**  
 **$\beta$ -THALASSEMIA MAJOR**

Mutations in globin genes cause thalassemias. Beta thalassemia ( $\beta$ -thalassemia) syndromes are a group of hereditary disorders characterized by a genetic deficiency in the synthesis of beta-globin chains. In the homozygous state,  $\beta$ -thalassemia (i.e. thalassemia major) causes severe, transfusion-dependent anemia. In the heterozygous state, the  $\beta$ -thalassemia trait (i.e. thalassemia minor) causes mild to moderate microcytic anemia. Patients in whom the clinical severity of the disease lies between that of thalassemia major and thalassemia minor are categorized as having thalassemia intermedia. Several different genotypes are associated with thalassemia intermedia. Hemoglobin (Hb) E, a common Hb variant found in Southeast Asia, is associated with a  $\beta$ -thalassemia phenotype, and this variant is included in the  $\beta$ -thalassemia category of diseases.

Complications associated with  $\beta$ -thalassemia, aside from the aforementioned anemia, are as follows:

- Extramedullary hematopoiesis
- Asplenia secondary to splenectomy
- Medical complications from long-term transfusion therapy - Iron overload and transfusion-associated infections (e.g. hepatitis)
- Increased risk for infections resulting from asplenia (e.g. encapsulated organisms such as pneumococcus) or from iron overload (e.g. Yersinia species)
- Cholelithiasis (e.g. bilirubin stones)

$\beta$ -thalassemia affects 1 or both of the  $\beta$ -globin genes. These mutations, by causing impaired synthesis of the  $\beta$ -globin protein component of Hb, result in anemia.  $\beta$ -thalassemia is inherited as an autosomal recessive disorder. The defect can be a complete absence of the  $\beta$ -globin protein (e.g.  $\beta$ -zero thalassemia) or a severely reduced synthesis of the  $\beta$ -globin protein (e.g.  $\beta$ -plus thalassemia).

In  $\beta$ -thalassemia major (i.e. homozygous  $\beta$ -thalassemia), the production of the  $\beta$ -globin chains is severely impaired because both  $\beta$ -globin genes are mutated. The severe imbalance of globin chain synthesis ( $\alpha \gg \beta$ ) results in ineffective erythropoiesis and severe microcytic hypochromic anemia. Target cells and hypochromia are prominent. The excess unpaired alpha-globin chains aggregate to form precipitates that damage red cell membranes, resulting in intravascular hemolysis. Premature destruction of erythroid precursors results in intramedullary death and ineffective erythropoiesis. The profound anemia typically is associated with erythroid hyperplasia and extramedullary hematopoiesis. Although  $\beta$ -thalassemia is caused by a genetic mutation in the  $\beta$ -globin gene which is located on chromosome 11, many additional factors influence the clinical manifestations of the disease. That is, the same mutations may have different clinical manifestations in different patients.

The factors below are known to influence the clinical phenotype

- Intracellular fetal Hb concentrations - the level of expression of fetal Hb (i.e. the expression level of the gamma-globin gene) in red blood cells determines, in part, the severity of the disease. Patients with high fetal Hb have milder disease.

- Coinheritance of alpha thalassemia - patients with coinheritance of alpha thalassemia have a milder clinical course because they have a less severe alpha-beta chain imbalance.
- Coexistence of sickle cell trait - the coexistence of sickle cell trait and  $\beta$ -thalassemia is a major and symptomatic hemoglobinopathy with most of the symptoms and complications of sickle cell disease. Unlike sickle cell trait, in which most Hb is Hb A (AS), S is the dominant Hb (SA) and usually constitutes about 60% or more of the circulating Hb, depending on the transfusion status of the patient and the nature of the coexisting  $\beta$ -thalassemia mutation (i.e. beta-zero vs beta-plus).

### Epidemiology

$\beta$ -thalassemia genes are reported throughout the world, although more frequently in Mediterranean, African, and Southeast Asian populations. Patients of Mediterranean extraction are more likely to be anemic with thalassemia trait than Africans because they tend to have  $\beta$ -zero thalassemia rather than  $\beta$ -plus thalassemia. The genetic defect in Mediterranean populations is caused most commonly by (1) a mutation creating an abnormal splicing site or (2) a mutation creating a premature translation termination codon. Southeast Asian populations also have a significant prevalence of Hb E and alpha thalassemia. African populations more commonly have genetic defects leading to alpha thalassemia. The manifestations of the disease may not be apparent until a complete switch from fetal to adult Hb synthesis occurs. This switch typically is completed by the sixth month after birth.

### Prognosis

The prognosis of patients with thalassemia major is highly dependent on the patient's adherence to long-term treatment programs, namely the hyper-transfusion program and lifelong iron chelation. Allogeneic bone marrow transplantation may be curative.

### History and Physical Examination

In patients with  $\beta$ -thalassemia major, the physical findings are related to severe anemia, ineffective erythropoiesis, extramedullary hematopoiesis, and iron overload resulting from transfusion and increased iron absorption. The skin may show pallor from anemia and jaundice from hyperbilirubinemia, and the skull and other bones may be deformed secondary to erythroid hyperplasia with intramedullary expansion and cortical bone thinning. The extremities may demonstrate skin ulceration. Heart examination may reveal findings of cardiac failure and arrhythmia, related to either severe anemia or iron overload. Abdominal examination may reveal changes in the liver, gallbladder, and spleen. Hepatomegaly related to significant extramedullary hematopoiesis typically is observed. Patients who have received blood transfusions may have hepatomegaly or chronic hepatitis due to iron overload. The gallbladder may contain bilirubin stones formed as a result of the patient's lifelong hemolytic state. Splenomegaly typically is observed as part of the extramedullary hematopoiesis or as a hypertrophic response related to the extravascular hemolysis. In addition to cardiac dysfunction, hepatomegaly, and hepatitis, iron overload can also cause endocrine dysfunction, especially affecting the pancreas, testes, and thyroid. Transfusion-associated viral hepatitis resulting in cirrhosis or portal hypertension also may be seen.

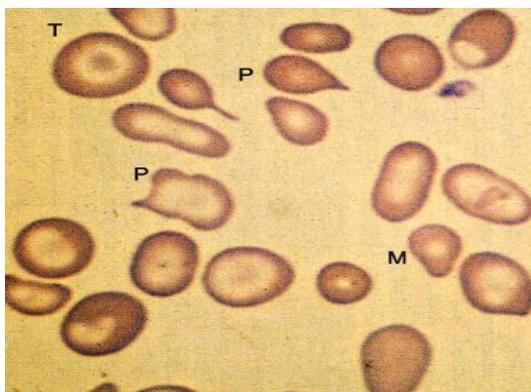
### Differential Diagnoses

- Alpha Thalassemia
- Anemia of Chronic Disease and Renal Failure
- Iron Deficiency Anemia
- Sideroblastic Anemias
- Lead Nephropathy

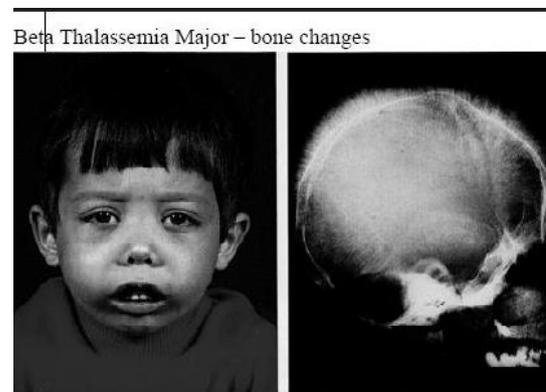
### Laboratory Studies

- Heinz bodies, which represent inclusions within RBCs consisting of denatured hemoglobin (Hb), may also be seen in the peripheral blood.
- Free erythrocyte porphyrin (FEP) tests may be useful in situations in which the diagnosis of  $\beta$ -thalassemia minor is unclear. The FEP level is normal in patients with the  $\beta$ -thalassemia trait, but it is elevated in patients with iron deficiency or lead poisoning.

- Alpha thalassemia is characterized by genetic defects in the alpha-globin gene, and this variant has features similar to beta thalassemia. Patients with this disorder have normal Hb A2 levels. Establishing the diagnosis of the alpha thalassemia trait requires measuring either the alpha-beta chain synthesis ratio or performing genetic tests of the alpha-globin cluster (using Southern blot or PCR assay tests).
- Iron studies (iron, transferrin, and ferritin) are useful in excluding iron deficiency and the anemia of chronic disorders as the cause of the patient's anemia.
- Evidence of hemolysis in the form of indirect hyperbilirubinemia, low haptoglobin, and elevated lactate dehydrogenase may be seen as a result of ineffective erythropoiesis and consequent destruction of these RBCs.
- Patients may require a bone marrow examination to exclude certain other causes of microcytic anemia. Physicians must perform an iron stain (Prussian blue stain) to diagnose sideroblastic anemia (ringed sideroblasts).
- The Mentzer index is defined as mean corpuscular volume per red cell count. An index of less than 13 suggests that the patient has the thalassemia trait, and an index of more than 13 suggests that the patient has iron deficiency.



Peripheral smear from a patient with  $\beta$ -zero thalassemia major showing marked microcytosis (M) and anisopoikilocytosis (P). Target cells (T) and hypochromia are prominent



### Treatment

Treatment for patients with thalassemia major includes chronic transfusion therapy, iron chelation, splenectomy, allogeneic hematopoietic transplantation, and supportive measures. Emerging therapies include pharmacologic agents that induce fetal hemoglobin, Jak2 inhibitors to reverse splenomegaly, hepcidin-related compounds to improve iron metabolism, and gene therapy aimed at delivering the beta globin gene into cells by a viral vector.

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### References

1. <http://emedicine.medscape.com/article/206490>
2. <https://www.google.co.za/#q=beta+thala+major+images>

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### Questions

1. Discuss the clinical features associated with  $\beta$ -thalassemia major.
  2. Discuss the differential diagnosis of  $\beta$ -thalassemia major.
  3. Discuss the lab findings in  $\beta$ -thalassemia major.
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