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Skeletal and extraskeletal manifestations of mixed alpha and beta thalassemia

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A 33-year-old male with known thalassemia intermedia presented with acute mid-back pain. Radiography and MRI were useful to evaluate the extent of iron deposition and assess for complications (such as cirrhosis) of the disease.

Case report

A 33-year-old male of Indian and African descent with known thalassemia intermedia presented to his hematologist's office with acute mid-back pain after lifting boxes overhead. His past medical history was significant for mixed α and β thalassemia intermedia complicated by iron overload, endocrinopathy, osteoporosis, and right ulna and radius fractures in 2008. The patient requires at least three blood transfusions per year for severe anemia. Mixed α and β thalassemia has shown to have better prognosis and milder clinical course because of less α chain imbalance (1, 2).

Lumbar radiographs demonstrated severe osteopenia, hepatomegaly, splenomegaly, and a wedge-compression fracture of the T12 vertebral body (Fig. 1). MRI demonstrated diffusely hypointense bone marrow on the T1- and T2-weighted images, consistent with red-marrow activation secondary to anemia and iron deposition (Fig. 2). An enlarged, diffusely hypointense liver was seen on the T1-weighted images, consistent with iron deposition (Fig. 3). A DEXA scan from January 2010 reported a lumbar Z score of -4.9, consistent with severe osteoporosis.

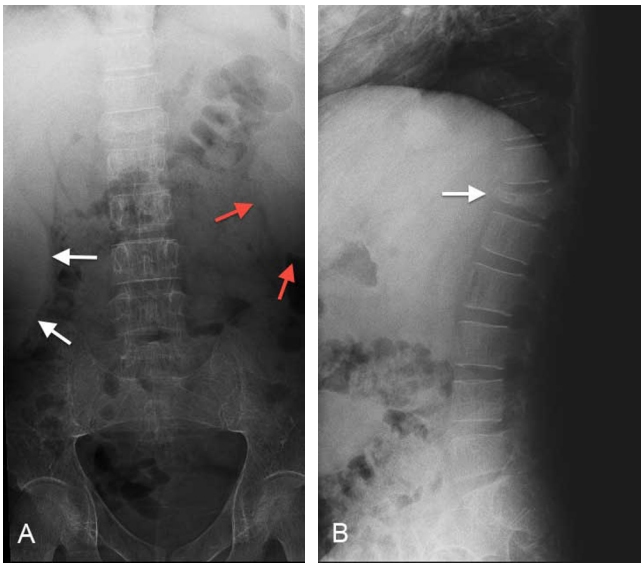

Figure 1. 33-year-old male with thalassemia intermedia. AP and lateral lumbar radiographs show severe osteopenia, hepatosplenomegaly, and T12 compression fracture.

Discussion

Thalassemia is a hemoglobinopathy characterized by abnormal globin production of the α globin chain, β globin chain, or both (3). It is one of the most common genetic disorders worldwide, with approximately five percent of the population carrying the globin variant, including 1.7% of the population who are heterozygous for the α and β thalassemia trait (3, 4). Men and women are equally affected by thalassemia, and it occurs in 4.4 of every 10,000 births (3). Thalassemias can occur in any population. However, α thalassemia is more common in Mediterranean countries,

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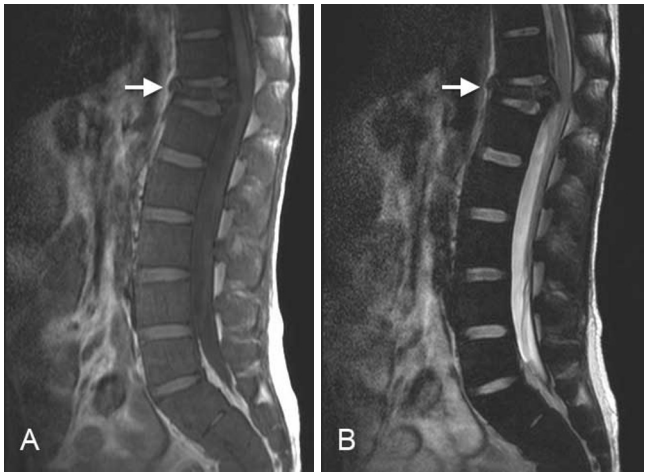

Figure 2. 33-year-old male with thalassemia intermedia. Sagittal T1- and T2-weighted images show T12 compression fracture and diffusely hypointense marrow.

Africa, the Middle East, and southeast Asia. Similarly, β thalassemia is commonly seen in Mediterranean, Middle Eastern, South Asian, and Southeast Asian countries (3, 4).

Patients with heterozygotes have a mild microcytic anemia, and those with homozygotes have thalassemia intermedia or major (depending on the clinical severity). Beta thalassemia major patients require blood transfusions from an early age, leading to growth failure, bony deformities, pathologic fractures, hepatosplenomegaly, and jaundice. Clinical manifestations of β thalassemia intermedia range from chronic hemolytic anemia with mild symptoms to transfusion-dependent disease with a severity similar to thalassemia major (3, 4). Ferritin levels are commonly used to monitor iron overload. Improved survival has been shown when ferritin levels are less than 2500mg/ml. However, this value is unreliable when liver disease is present (3, 4).

Because of the variable genetics and complex physiologic responses to the disease and therapy, thalassemias have clinical variability. The severity of the disease is directly related to the amount of globin chain imbalance. In β thalassemia, α chains accumulate in the marrow and in red blood cells, leading to ineffective marrow erythropoiesis, hemolysis, and a hypochromic microcytic anemia. Alpha thalassemia also has hemolysis; however, less deficiency in erythropoiesis is seen, as the β chains are soluble in the marrow. To compensate for the anemia, those affected by β thalassemia have increased hemoglobin A2 ($\alpha_2\delta_2$) and hemoglobin F ($\delta_2\gamma_2$). Alpha thalassemia does not exhibit increased hemoglobins, as the α chain is limiting (3, 4).

Imaging findings in patients with thalassemias also vary depending on the severity of the disease and globin-chain imbalance (1). Visible features include progressive splenomegaly; facial, skull, and bone deformities; osteoporosis; and iron deposition within the liver, bone marrow, pancreas, myocardium, adrenal glands, and musculoskeletal system (3, 4).

Splenomegaly occurs secondary to extramedullary hematopoiesis (4). It may be also due to portal venous hypertension secondary to cirrhosis in these patients with iron deposition. Facial, skull, and bone deformities are seen secondary to ineffective erythropoiesis and chronic hemolysis, which leads to secondary bone-marrow stimulation and results in bone-marrow expansion and deformity (4, 5). These facial, skull, and bone deformities can in turn lead to pathologic fractures (4, 5).

Osteoporosis has a multifactorial pathogenesis in thalassemias, including bone-marrow expansion, endocrine dysfunction, and iron overload. Marrow expansion secondary to red-marrow activation from the anemia mechanically interrupts bone formation and leads to cortical thinning and increased fragility. Hemosiderosis of the pituitary gonadotrophic cells and gonads causes a hypogonadotrophic state, in which there is high bone turnover with an enhanced resorptive phase (4, 5).

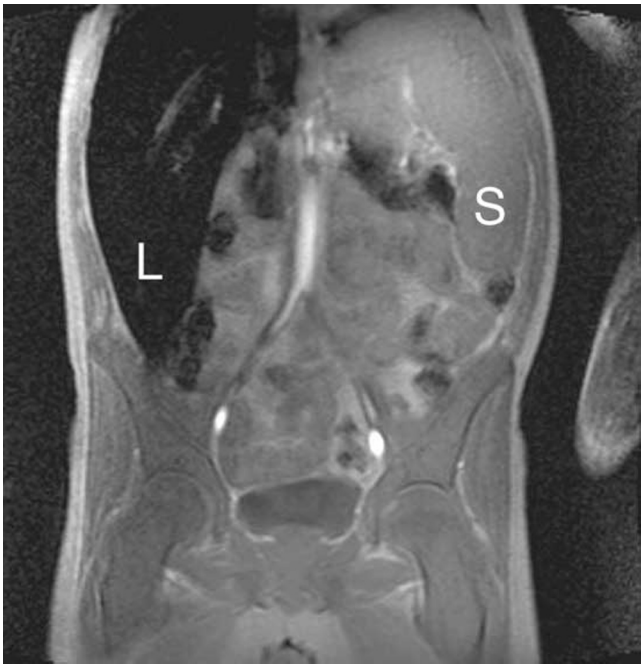

Figure 3. 33-year-old male with thalassemia intermedia. T1-weighted coronal image shows markedly enlarged, hypointense liver and splenomegaly.

Iron deposition is the most important cause of morbidity and mortality in thalassemia, and it can be quite striking on imaging. This iron deposition is seen secondary to the ineffective erythropoiesis, which triggers increased gastrointestinal absorption of iron due to increased marrow demand. The iron distribution is similar to that in patients with primary (genetic) hemachromatosis, where deposition is seen within the liver, thyroid, adrenal glands, pituitary gland, pancreas, myocardium, and musculoskeletal system. However, in patients with thalassemia, iron deposition is also seen within the bone marrow, unlike patients with primary

hemachromatosis. The spleen may be spared from iron deposition in patients with thalassemia even with repetitive transfusions, likely secondary to the impared reticuloendothelial cell function. The iron deposition in the liver parenchyma over time leads to cirrhosis. An increased rate of hepatocellular carcinoma has been demonstrated in these patients. Other complications include diabetes mellitus, hypoparathyroidism, hypothalamic-pituitary dysfunction with hypothyroidism, and hypogonadism (6). The most lethal complication is heart failure (1, 4, 6).

Iron deposition on MR imaging demonstrates decreased signal intensity on the T1-weighted, T2-weighted, and T2* images. If liver signal intensity is less than that of muscle, this indicates iron deposition. MR imaging is useful in thalassemia patients to evaluate the extent of iron deposition and to assess for complications of the disease, such as cirrhosis. MR imaging is the least invasive and most sensitive and specific imaging technique for the diagnosis and evaluation of iron deposition in thalassemia (6). It can be used to follow the effects of phlebotomy therapy. Quantitation of hepatic iron deposition is possible but needs liver biopsy samples and diligent attention to MRI technique (7). Iron deposition is demonstrated by loss of signal intensity within the organs on the T1-weighted images secondary to the shortened longitudinal relaxation time; on the T2-weighted images secondary to the transverse relaxation time; and on the T2* images secondary to the transverse relaxation time (as affected by magnetic field inhomogeneity). The effects of iron deposition are most apparent on the T2* images, and the loss of signal intensity is proportional to the amount of iron deposition (6).

References

1. Reynolds J, Pritchard JA, Ludders D, Mason RA. Roentgenographic and clinical appraisal of sickle cell beta-thalassemia disease. *Am J Roentgenol Radium Ther Nucl Med.* 1973 Jun;118(2):378-400. [PubMed]
2. Brasch RC, Wesbey GE, Gooding CA, Koerper MA. Magnetic resonance imaging of transfusional hemosiderosis complicating thalassemia major. *Radiology*. 1984 Mar;150(3):767-71. [PubMed]
3. Muncie HL Jr, Campbell J. Alpha and beta thalassemia. *Am Fam Physician*. 2009 Aug 15;80(4):339-344. [PubMed]
4. Rund D, Rachmilewitz E. B-thalassemia. *N Engl J Med.* 2005 Sep 15;353(11):1135-46. [PubMed]
5. Cassady JR, Berdon WR, Baker DH. The "typical" spine changes of sickle-cell anemia in a patient with thalassemia major (Cooley's anemia). *Radiology*. 1967 Dec;89(6):1065-8. [PubMed]
6. Queiroz-Andrade M, Blasbalg R, Ortega CD, Rodstein MA, Baroni RH, Rocha MS, Cerri GG. MR imaging findings of iron overload. *Radiographics*. 2009 Oct;29(6):1575-89. [PubMed]
7. Fisher A, Seligman ES. Body MR techniques and MR of the liver. In Seligman ES, *Body MRI*. Philadelphia, PA: Elsevier Saunders; 2005: 33-6.