Thoracic Manifestations of Hemolytic Anemia

Exhibit Category: Educational

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Author Disclosures

None
Learning Objectives

• Review the most common hereditary hemolytic anemias which have associated cardiothoracic manifestations:
  • Sickle cell disease
  • Thalassemia
  • Hereditary spherocytosis

• Describe imaging findings in hemolytic anemia:
  • Acute chest syndrome
  • Osteoarticular abnormalities
  • Extramedullary hematopoiesis
  • Chronic lung disease

• Describe the cardiac imaging findings of hemolytic anemia:
  • Pulmonary hypertension
  • Cardiomyopathy
    • Secondary hemochromatosis
    • Ischemic cardiomyopathy and myocardial infarction
Overview

- Hemolytic anemias are typically categorized as either \textit{inherited} or \textit{acquired}

<table>
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<tr>
<th>Inherited</th>
<th>Acquired</th>
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<tr>
<td>Sickle cell anemia*</td>
<td>Autoimmune hemolytic anemia (AIHA)</td>
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<td>Thalassemia*</td>
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<td>Hereditary Spherocytosis*</td>
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<td>Glucose Phosphate Dehydrogenase (G6PD) deficiency</td>
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<td>Pyruvate Kinase Deficiency</td>
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* Indicates those with imaging features.
Overview: Sickle Cell Disease

- Abnormal hemoglobin “S” results from inheritance of two genes affecting both B-globin subunits which are replaced with hemoglobin S
  - When deoxygenated, hemoglobin S becomes distorted, causing sickling and impairing microvascular flow

- Clinical manifestations:
  - Pulmonary: Acute chest syndrome
  - Neurologic: Stroke
  - Musculoskeletal: Dactylitis, ulcerations, osteomyelitis, osteonecrosis
  - Genitourinary: Renal insufficiency, spontaneous abortion, priapism
  - Gastrointestinal: Liver disease, splenic sequestration, cholelithiasis

- Thoracic imaging manifestations:
  - Acute chest syndrome
  - Pulmonary hypertension
  - Chronic lung disease
  - Diffuse bone sclerosis / osteonecrosis

Sickled RBCs lead to vascular occlusion.

Steinberg. NEJM. 1999
Inati et al. Pediatric Annals. 2008 (figure)
Overview: Thalassemia

- Results from absent genes for alpha or beta globin
  - Beta thalassemia is more common than alpha thalassemia
  - Clinical severity depends upon number of absent genes
  - Most prevalent in the Mediterranean basin, Middle East, Indian subcontinent, and Southeast Asia

- Clinical manifestations:
  - Cardiac: secondary hemochromatosis, heart failure
  - Endocrine: hypothyroidism, hypogonadism, diabetes
  - Gastrointestinal: cholelithiasis

- Thoracic imaging manifestations:
  - Iron cardiotoxicity
  - Pulmonary hypertension
  - Extramedullary hematopoiesis

Shawky R et al Egyptian Journal of Medical Human Genetics 2011 (figure)
Overview: Hereditary Spherocytosis

- Autosomal dominant disease resulting in sphere-shaped erythrocytes.
  - Most common inherited form of hemolysis in north Europe and North America
  - Common molecular defects include proteins spectrin, ankyrin, band 3 protein, and protein 4.2
  - Dysfunctional membrane proteins interfere with the cellular transit through capillaries
  - Abnormal erythrocytes prone to rupture and degradation by the spleen

- Clinical complications:
  - Gastrointestinal: Cholelithiasis
  - Hematologic: Hemolytic, aplastic, and megaloblastic crises

- Thoracic imaging manifestations:
  - Iron cardiotoxicity
  - Extramedullary hematopoiesis
  - Pulmonary hypertension

Comparison of normal biconcave erythrocytes with central pallor with spherocytes in a peripheral blood smear.

Perrotta et al. Lancet. 2008
Shah et al. Pediatrics in Review. 2004 (figure)
Acute Chest Syndrome in Sickle Cell Disease

- **Definition:**
  - New pulmonary infiltrate in association with fever, chest pain, wheezing, or cough

- **Etiologies:**
  - Infection with RSV, Chlamydia, Mycoplasma, Staphylococcus aureus, or Streptococcus pneumoniae.
  - Fat embolism
  - Microinfarctions caused by intravascular occlusions

- **Imaging findings:**
  - Atelectasis, consolidation, mosaic attenuation, pleural effusion

Sickle cell patient with acute chest syndrome manifested radiographically as diffuse bilateral consolidations

Vichinsky EP et al. NEJM. 2000
Acute Chest Syndrome in Sickle Cell Disease

Two different patients with acute chest syndrome due to pneumonia

- Patchy consolidation
- Scattered ground glass opacities
Acute Chest Syndrome in Sickle Cell Disease

Another case of acute chest syndrome secondary to pneumonia in sickle cell disease

Bilateral geographic ground glass opacities
Acute Chest Syndrome in Sickle Cell Disease

- Fat Embolism
  - Up to 9% of acute chest syndrome
  - Result of bone marrow necrosis (femurs and pelvis most common) with release of fat, cells, and tiny fragments of bone into blood

- Imaging findings:
  - Patchy consolidation
  - On CT, no filling defects in pulmonary arteries
  - One of three patterns on CT:
    - Geographic ground glass
    - Ground glass with septal thickening (“crazy paving”)
    - Nodular opacities

Vichinsky EP et al. NEJM. 2000
Chronic Lung Disease in Sickle Cell Disease

- **Clinical Manifestation:**
  - Mild restrictive lung disease with decreased diffusion capacity.
  - Prevalence as high as 4%

- **Etiologies:**
  - Associated with recurrent episodes of acute chest syndrome, leading to lung scarring

- **Imaging findings:**
  - Lower-lobe-predominant scattered scarring.
  - Severity is correlated to number of episodes of acute chest syndrome
    - Advanced disease is rare.

Chronic Lung Disease in Sickle Cell Disease

Sickle cell disease with reticular scarring in lower lungs
Osteoarticular Involvement in Sickle Cell Disease

- Bones are the second most commonly affected organ after spleen.
- Thoracic manifestations include:
  - Medullary necrosis
  - Vertebral body collapse
  - Osteomyelitis
- Sickling in the bone microcirculation results in infarction and necrosis.
- Presents as acute painful crises

Two sickle cell disease patients with diffuse bone sclerosis (top) and humeral head osteonecrosis (bottom).

Osteoarticular Involvement in Sickle Cell Disease

• "H-shaped" vertebrae
• Caused by central endplate collapse
  • Medullary hyperplasia causes demineralization, leading to biconcave endplate deformities.

Two patients with sickle cell disease and central endplate collapse ("H-shaped" vertebrae).

Extramedullary Hematopoiesis

- Definition: proliferation of hematopoietic cells outside of the bone marrow
- Etiology: failure of hematopoiesis within the bone marrow
- Imaging appearance:
  - Soft tissue mass with well defined borders
  - Paravertebral location, can be bilateral or unilateral
  - Contrast enhancement on both CT and MR
- Association:
  - All hemolytic anemias

Patient with beta thalassemia and bilateral paraspinal masses (red arrows) from extramedullary hematopoiesis.
Extramedullary Hematopoiesis

Contrast enhanced CT correlated with MRI shows bilateral paraspinal masses

T2 black-blood MRI with fat saturation

(Same patient as in previous slide)
Cardiac Manifestations of Hemolytic Anemia

• Pulmonary hypertension
  • Present in ~30% of sickle cell disease patients and 75% of thalassemia major patients
  • Thought to be secondary to pulmonary arteriopathy with increased vascular resistance
  • Causes increased mortality

• Cardiomyopathy
  • Most often associated with sickle cell disease and beta thalassemia
  • Secondary hemochromatosis can be evaluated with MRI T2* analysis
Pulmonary Hypertension

- Increases risk of all cause mortality

- Multifactorial etiology:
  - Chronic anemia
  - Nitric oxide deficiency
  - Hypercoagulable state
  - LV dysfunction
  - Chronic lung disease

Beta thalassemia patient with pulmonary hypertension

Mehari A et al. Am J Respir Crit Care Med. 2013
Pulmonary Hypertension

• Imaging Findings:
  • Main pulmonary artery (MPA) diameter
    • MPA diameter > 29 mm
    • MPA: Aorta diameter ratio > 1.0

Beta thalassemia patient with pulmonary hypertension
MPA > 29 mm

Sickle cell disease patient with pulmonary hypertension
MPA:Aorta ratio > 1
Right Ventricular Dysfunction

- Usually due to a combination of:
  - Pulmonary hypertension
  - Left ventricular dysfunction (both systolic and diastolic)

- Imaging Findings:
  - Enlarged right ventricular size and decreased function
  - Interventricular septum displacement

Thalassemia patient with anemia, iron overload, and decreased biventricular systolic function (LVEF=47% and RVEF=33%).

Left Ventricular Dysfunction

- High output state results from
  - Hemolysis leading to bone marrow expansion
  - Peripheral vasodilation from
    - Liver disease (viral infection, iron overload, etc.)
    - Elastic disorder of blood vessels
- Imaging Appearance:
  - Left ventricular dilation and hypertrophy
  - Eventually leads to heart failure.
Left Ventricular Dysfunction

• Left ventricular dysfunction.
  • Vasculopathy / myocardial ischemia
    • Results from hemolysis-induced nitric oxide deficiency and hypercoagulable state, leading to chronic microvascular infarcts.
  • Imaging findings
    • Typically do not see large vessel occlusions.
    • Myocardial fibrosis from small vessel disease results in patchy areas of late gadolinium enhancement.

Pepe, Alessia et al. **Myocardial fibrosis by late gadolinium enhancement cardiac magnetic resonance and hepatitis C virus infection in thalassemia major patients.** Journal of Cardiovascular Medicine. 16(10):689, October 2015. (Figure)
Left Ventricular Dysfunction

• Caused by secondary hemochromatosis
  • Results from
    • Multiple blood transfusions
    • Hemolysis
    • Increased intestinal absorption.
  • Iron accumulation results in peroxidative cell injury with LV diastolic and systolic dysfunction.

• Imaging findings:
  • Myocardial iron shortens T2* relaxation time.
  • Defined as a T2*<33.3 +/- 7.8 msec measured by ROI in the septum.
  • Pancreatic and hepatic T2* values are frequently obtained
    • Pancreatic > 10 msec is a negative predictor for cardiac iron loading,
    • T2* < 10 msec has a positive predictive value of 60% for current or future cardiac iron loading

T2* analysis in patient with thalassemia and iron overload

Summary

• Hemolytic anemias can be acquired or congenital.
• Thoracic manifestations include:
  • Non-cardiac findings:
    • Acute chest syndrome in sickle cell disease secondary to infections, fat emboli, or microvascular occlusions
    • Unique osteoarticular findings in sickle cell disease (osteonecrosis, H-shaped vertebrae)
    • Extramedullary hematopoiesis in all hemolytic anemias
  • Cardiac
    • Pulmonary hypertension
    • Right and left ventricular dysfunction
References and Suggested Reading:


