Marrow: Red, Yellow and Bad

R. Paul Guillerman, MD
Associate Professor of Radiology
Baylor College of Medicine
Department of Pediatric Radiology
Texas Children’s Hospital
Houston, Texas
Disclosure of Commercial Interest

Neither I or a member of my immediate family have a financial relationship with a commercial organization that may have an interest in the content of this educational activity.
Topics

- Normal Marrow Composition, Conversion, and Variants
- Marrow Hyperplasia, Reconversion, and Reconstitution
- Marrow Infiltration and Deposition Disorders
- Marrow Failure and Depletion Disorders
Normal Marrow Composition, Conversion, and Variants
Composition of Bone Marrow

Cancellous trabeculae
Stromal tissue
Hematopoietic cells
Fat
Red Marrow Composition

- Color due to hemoglobin in erythroid cells
- Active in hematopoiesis
- Highly vascularized
Red Marrow Composition

- Hematopoietic cellularity diminishes from near 100% at birth to 60% by adulthood
- Fat content increases with age
- By adulthood, composed of 40% fat, 40% water, 20% protein

Yellow Marrow Composition

- Color due to carotenoids in fat droplets
- Minimal hematopoiesis
- Paucity of vasculature

Yellow Marrow Composition

- Predominantly fat in adipocytes
- 95% of cells are adipocytes
- By adulthood, composed of 80% fat, 15% water, 5% protein
Marrow Signal Intensity on MRI

- Largely depends on the proportion of fat in the marrow
- Yellow marrow signal intensity similar to subcutaneous fat on T1-W sequences
Marrow Signal Intensity on MRI

- Red marrow signal intensity equal to or lower than skeletal muscle on T1-W sequences in neonates

- During childhood, red marrow signal intensity on T1-W sequences becomes equal to or slightly greater than skeletal muscle and the inter-vertebral discs, but much less than subcutaneous fat
Marrow Signal Intensity on MRI

- Red marrow signal intensity higher than yellow marrow and slightly higher than skeletal muscle on fat-sat T2-W and STIR sequences

- Red marrow signal dropout greater than yellow marrow on opposed-phase gradient echo sequences
Marrow Signal Intensity on MRI

- Gadolinium-enhancement greater in red marrow than in yellow marrow
- ADC values higher in red marrow than in yellow marrow
Age-Related Physiologic Pattern of Red to Yellow Marrow Conversion
Age-Related Physiologic Pattern of Red to Yellow Marrow Conversion

- Older = fatter
Age-Related Physiologic Pattern of Red to Yellow Marrow Conversion

- Older = fatter
- Appendicular to axial, distal to proximal, diaphyseal to metaphyseal, central to endosteal

Blebea Semin Nucl Med 2007
Age-Related Physiologic Pattern of Red to Yellow Marrow Conversion

- Soon after ossification in the epiphyses and apophyses
Age-Related Physiologic Pattern of Red to Yellow Marrow Conversion

- No sex difference, except boys get fat heads quicker

Waitches AJR 1994
Red to Yellow Marrow Conversion
T1-Weighted MRI

3-month-old

10-month-old
Red to Yellow Marrow Conversion
T1-Weighted MRI

6-year-old

16-year-old
Adult Distribution of Red Marrow

- Residual red marrow in primarily in the axial skeleton
Physiologic Red Marrow Residua in the Appendicular Skeleton

- Spotty or flame-shaped with base near physis
Physiologic Red Marrow Residua in the Appendicular Skeleton

- Slightly higher signal intensity than skeletal muscle
Tarsal Patchy Marrow Signal Alterations

- Seen in 60% of asymptomatic children and adolescents
- Calcaneus, talus > navicular, cuneiform > cuboid, MTs
- Sub-endosteal, bilateral and mostly symmetric
Tarsal Patchy Marrow Signal Alterations

- ? Red marrow residua
- ? Stress response to altered biomechanics of growth
Marrow Hyperplasia, Reconversion, and Reconstitution
7-year-old girl with sickle cell disease
Marrow Hyperplasia and Reconversion

- Replacement of yellow marrow by red marrow

- Conditions with increased hematopoiesis
  - Chronic hemolytic anemia (sickle cell, thalassemia)
  - Treatment with hematopoietic growth factors (G-CSF, GM-CSF, erythropoietin)
  - Increased oxygen demands or impaired oxygen delivery (smoking, high altitude residence, endurance athletics, cyanotic congenital heart disease)
  - Menorrhagia
  - Obesity
11-year-old girl with obesity and anemia

T1-W T2-W
12-year-old girl with sickle cell disease

- Reconversion occurs in reverse order of normal marrow conversion
17-year-old with right femoral Ewing sarcoma on chemotherapy
Hematopoietic Growth Factor Therapy (G-CSF, GM-CSF, Erythropoietin)

- Induces hematopoietic marrow hyperplasia and reconversion
Hematopoietic Growth Factor Therapy (G-CSF, GM-CSF, Erythropoietin)

- Low signal intensity on T1-W sequences can simulate or obscure neoplastic infiltration of the marrow
Transient Marrow Hyperplasia Induced by G-CSF

- Resolves 4-6 weeks after discontinuation of therapy
8-year-old with thalassemia, 75 days after bone marrow transplant

- Engraftment ensues 2-4 weeks after transplant, starting in the vertebrae

Guillerman Caffey's Pediatr Diag Imag Mosby 2008
8-year-old with thalassemia, 75 days after bone marrow transplant

- Engraftment complete by 3 months after transplant, but may not get full reconstitution of hematopoietic marrow
Marrow Infiltration and Deposition Disorders
5-year-old with shoulder pain, anemia and leukopenia
Acute Leukemia

- Diffuse low marrow signal intensity on T1-W sequences and high signal intensity on fat-suppressed T2-W and STIR sequences
- Bilateral symmetry may be misinterpreted as normal
- Marrow may appear normal if < 20% neoplastic cells
- ALL and AML cannot be reliably distinguished by MRI
6-year-old with fever, knee pain, and normal CBC
“Aleukemic” or “Subleukemic” Leukemia

- Masquerades as an infectious, rheumatologic or orthopedic disorder due to musculoskeletal complaints

Guillerman SPR Postgrad Course Syllabus 2005
“Aleukemic” or “Subleukemic” Leukemia

- MRI can suggest the diagnosis before leukocytosis or blasts appear in the peripheral blood

Guillerman SPR Postgrad Course Syllabus 2005
5-year-old with ALL

Pre-Therapy

Post-Induction Chemotherapy

T1-W

T1-W
Leukemia Therapy Response Evaluation

- Marrow fat fraction increases in patients responding to chemotherapy
Leukemia Therapy Response Evaluation

- Regenerating red marrow can be indistinguishable from residual or recurrent leukemia
- No routine role for MRI
Marrow infiltration by malignant cells decreases the extracellular water fraction and restricts diffusion.

Marrow ADC values increase with effective leukemia therapy related to cell membrane compromise and an increased ratio of extracellular to intracellular water.
Diffusion values in normal marrow are widely variable in childhood.

ADC values in untreated leukemia do not differ significantly from those in hyperplastic red marrow.
8-year-old with history of ALL
Leukemia Relapse Detection by MRI

- Can be detected by MRI several weeks before diagnosis by iliac bone marrow aspirate or biopsy, due to marrow sampling bias.

- Suggested by the finding of well-defined nodular lesions in the marrow.

- Must differentiate from marrow hyperplasia from G-CSF, osteonecrosis and stress injury related to osteopenia.
3-year-old with constipation
Metastatic Infiltration of the Marrow

- Usually multifocal, but can be diffuse, most commonly in neuroblastoma or rhabdomyosarcoma

- MRI and FDG-PET are comparable in diagnostic efficacy

- Easier to detect in yellow than in red marrow by MRI and FDG-PET
1-month-old with foot right sarcoma, marrow metastases
Metastatic Infiltration of the Marrow

- Since tumor infiltration tends to replace marrow fat, loss of red marrow signal intensity on opposed-phase MRI sequences suggests the absence of tumor infiltration.

- Gadolinium-enhanced sequences increase the specificity but not the sensitivity of MRI for marrow infiltration.

- Due to the effects of tumor treatment on the marrow, MRI is of limited utility in assessing for residual metastatic disease in the marrow.
5-year-old with anemia and limb pain

T1-W

T2*-W

Guillerman Caffey's Pediatr Diag Imag Mosby 2008
Gaucher Disease

- Diffuse marrow infiltration, patchy marrow infarction, Erlenmeyer flask deformities

Guillerman Caffey's Pediatr Diag Imag Mosby 2008
Gaucher Disease

- Glucocerebroside-laden histiocytes reduce the marrow signal intensity on T1-W and T2-W sequences.

- High signal intensity foci on fat-suppressed T2-W or STIR sequences may represent complicating infarction, osteomyelitis, or pathologic fracture.
Monitoring Gaucher Disease with MRI

- T1-W MRI of lumbar spine/femurs recommended every 1-2 yrs to assess enzyme replacement therapy response

10-years-old

12-years-old

T1-W MRI of lumbar spine/femurs recommended every 1-2 yrs to assess enzyme replacement therapy response
Monitoring Gaucher Disease with MRI

- Normal red to yellow marrow conversion confounds assessment of response to enzyme replacement therapy
18-year-old with history of AML

FFE T1-W
Iron Overload

- Most commonly a consequence of numerous blood transfusions
- Reduces marrow signal intensity, particularly on T2*-W gradient echo sequences, and on T1-W spin echo sequences at high iron concentrations
- May also manifest with a reduction in signal intensity in other components of the reticuloendothelial system, such as the liver and spleen
Marrow Depletion and Failure
17-year-old girl with pancytopenia

T1-W

Gad T1-W
Aplastic Anemia from Parvovirus B19 Infection

- Parvovirus B19 is directly cytotoxic to bone marrow progenitor cells

- Parvovirus B19 infection is particularly detrimental in conditions with shortened erythrocyte lifespan (e.g. sickle cell, thalassemia, spherocytosis, HIV)
Aplastic Anemia

- Can be idiopathic or due to infection, drug reaction

- Abnormal extent of high marrow signal intensity on T1-W sequences reflects diminished hematopoietic marrow

- Loss of high marrow signal intensity on T1-W sequences suggests transfusional hemosiderosis, regenerative hematopoietic marrow, or development of clonal disease (myelodysplastic syndrome or leukemia)
9-year-old with ALL in remission and knee pain
Osteonecrosis (Avascular Necrosis, Bone Infarction)

- Geographic shape with “double line” sign of outer sclerotic rim and inner rim of vascularized granulation tissue or chondroid metaplasia
Osteonecrosis

- Sequence of hemorrhage, edema, liquefactive necrosis, granulation, fibrosis and sclerosis

- Associated conditions marked by adipogenesis, impaired perfusion, or osteocyte apoptosis
  - Sickle cell disease
  - Gaucher disease
  - Chronic renal failure
  - Bone marrow transplantation
  - Steroid therapy
  - Antiretroviral therapy for HIV infection

- Unusual in hematopoietic marrow, except in patients with hemoglobinopathies
ALL patient with bone pain and fever

T1-W  
Gad T1-W FS
Bone Marrow Necrosis

- Geographic lesions with peripheral enhancement and variable central signal intensity
Bone Marrow Necrosis

- Necrosis of myeloid elements, marrow fat and medullary stroma but preservation of bony trabeculae
- Distinct from osteonecrosis (less axial, less extensive)
- Associated with malignancy (especially ALL), sickle cell disease, infection
- Due to microvascular occlusion
19-year-old with sickle cell disease, acute leg pain and fever
Acute Bone Marrow Infarction

- Sequestered packed rbc’s increase T1 relaxivity leading to high signal intensity on fat sat T1-W sequences
15-year-old with sickle cell disease and acute bone marrow infarction

- Rim enhancement develops after several days and thickness of rim increases over time
Sickle Cell Acute Bone Marrow Infarction

- Sickle cell disease predisposes to Staphylococcus and Salmonella bone infection

- Acute infarction and acute osteomyelitis can present identically with pain, swelling, fever, and leukocytosis

- Marrow edema and extra-osseous fluid collections commonly seen on MRI in both infarction and infection
Sickle Cell Acute Bone Marrow Infarction

- Bright marrow signal intensity on fat sat T1-W sequences favors infarction over infection.
- Infarction 50X more common than infection.
- Detectable by MRI in 1/3 of acute pain crises.
Teenager with wrist pain and erythematous subcutaneous nodules
Pancreatitis-Associated Marrow Fat Necrosis

- Subcutaneous panniculitis, intra-osseous fat necrosis and polyarthritis

- Most commonly involves ankles, knees, and wrists

- Occurs in 2-3% of cases of pancreatitis

- 2/3 with mild or no abdominal symptoms, leading to delay in diagnosis

- ? Due to lipolysis by pancreatic enzymes
15-year-old, post-XRT for extraosseous supraclavicular Ewing sarcoma

Guillerman Caffey's Pediatr Diag Imag Mosby 2008
Radiation Therapy Effect on Marrow

- Marrow signal intensity alteration sharply delimited by the radiation therapy portal
- Edema and hemorrhage in the acute phase
- Replacement of hematopoietic marrow by fat and fibrosis in the chronic phase
- In young patients and at doses < 30-40 Gy, hematopoietic marrow may regenerate and fatty replacement may be incomplete
9-year-old autistic boy with refusal to walk, anemia, elevated homocysteine
Diet consists only of oatmeal
Gelatinous Transformation of the Marrow

- Focal loss of hematopoietic cells, fat cell atrophy, and deposition of gelatinous mucopolysaccharides rich in hyaluronic acid

- Associated with radiation therapy and cachexia (anorexia nervosa, cancer, AIDS)

- “starvation marrow”
Awareness of deviations from the normal age-related process of conversion of hematopoietic to fatty marrow is essential for recognizing many marrow pathologies on MRI in children.

MRI is valuable for diagnosing, assessing response to therapy, and detecting complications of treatment for certain conditions involving the marrow.

While a specific diagnosis may not be possible, recognition of patterns of marrow signal abnormality on MRI can refine the differential diagnosis.