Since the first reports of MRI of the bone marrow in children were published in the mid 1980’s, MRI has become the primary imaging modality used to evaluate the marrow. MRI provides a noninvasive method for visualizing a large sample of the marrow and detecting alterations in its chemical and cellular composition related to a variety of physiologic and pathologic processes. MRI reveals information about bone marrow inaccessible or difficult to biopsy.

On gross examination, bone marrow may be red (due to hemoglobin in the erythrocytes and their precursors) or yellow (due to the presence of carotenoid derivatives dissolved in fat droplets in adipocytes). Red marrow is active in hematopoiesis and highly vascularized, while yellow marrow largely composed of fat. The marrow signal intensity on spin echo sequences is primarily determined by the proportion of fat and water in the marrow. The signal intensity of yellow marrow is similar to subcutaneous fat on conventional spin echo (CSE) T1-weighted sequences. In neonates, red marrow is highly cellular and contains minimal fat, resulting in low signal intensity on CSE T1-weighted sequences. Red marrow cellularity decreases and fat content progressively increases through childhood, with red marrow signal intensity equal to or slightly greater than the signal intensity of muscle and intervertebral discs, but much less than the signal intensity of subcutaneous fat on CSE T1-weighted sequences. Red marrow exhibits higher signal intensity than yellow marrow and slightly higher signal intensity than muscle on fat-suppressed fast spin echo (FSE) T2-weighted and STIR sequences. Enhancement of the marrow by gadolinium contrast is greater in children than in adults, greater in the metaphyses than in the epiphyses, and greater in the red marrow than in the yellow marrow. Magnetic susceptibility effect from trabecular bone and iron leads to a lower signal intensity of the marrow on gradient echo T2*-weighted sequences than on spin echo sequences [1,2,3].

CSE T1-weighted and fat-suppressed FSE T2-weighted or STIR sequences constitute a basic MRI protocol for the detection and characterization of most marrow lesions. Gadolinium-enhanced T1-weighted sequences increase the cost and duration of the MRI exam while providing only modest incremental added sensitivity for marrow lesions, and should be reserved for cases with unclear findings on the noncontrast sequences. Gradient echo sequences are valuable for the assessment of the iron content of the marrow. Coronal and sagittal imaging planes facilitate evaluation of the symmetry and the longitudinal pattern of the marrow signal intensity and are generally preferable to the axial imaging plane.

Conversion from hematopoietic to fatty marrow occurs in a predictable pattern,
i.e., from distal to proximal in the appendicular skeleton, from diaphyseal to metaphyseal in the long bones, at a faster pace in the appendicular skeleton than in the axial skeleton, and within a few months after the onset of ossification in the epiphyses and apophyses. Marrow conversion is observed earlier by MRI than by gross pathologic inspection, and is clearly depicted by T1-weighted spin echo sequences due to their high sensitivity for fat. Numerous publications detail the normal temporal and spatial sequence of conversion of hematopoietic to fatty marrow visible on MRI, and knowledge of the normal age-related changes in the distribution of hematopoietic and fatty marrow in the axial and appendicular skeleton is necessary for the recognition of abnormal conversion and reconversion patterns as well as the detection of infiltration of the marrow by tumors and other pathologic processes [4,5,6].

Abnormalities of bone marrow composition are easier to detect in fatty marrow than in hematopoietic marrow. Abnormal low signal intensity of the marrow on T1-weighted sequences and high signal intensity on T2-weighted or STIR sequences occurs in hematopoietic marrow hyperplasia (such as in hemolytic anemia or hematopoietic growth factor treatment), leukemia, lymphoma, myeloproliferative syndromes, and infiltration of the marrow by metastatic or inflammatory processes. Findings that favor low marrow signal intensity on T1-weighted sequences as representing physiologic hematopoietic marrow rather than a pathologic process include similar signal intensity to other areas of hematopoietic marrow on other sequences, signal intensity that is only slightly higher rather than much higher than muscle on fat suppressed FSE T2-weighted or STIR sequences, normal enhancement on Gadolinium-enhanced T1-weighted sequences, symmetry with the contralateral side, and no associated abnormalities of the cortical bone or extrasosseous soft tissues. However, a low grade infiltrative or edematous process of the marrow can be difficult or impossible to distinguish from hematopoietic marrow on MRI, particularly in settings where the hematopoietic marrow is extensive and hypercellular, such as in very young children and in states of marrow reconversion. Abnormal low signal intensity of the marrow on T1- and T2-weighted sequences occurs in myelofibrosis, osteopetrosis, and iron overload. Abnormal high signal intensity of the marrow on T1-weighted sequences occurs in aplastic anemia. Variable alterations in marrow signal intensity occur with medullary infarction, Gaucher disease, myelodysplastic syndromes, chemotherapy, radiation therapy, or marrow transplantation [3].

Marrow reconversion is the replacement of yellow marrow by hyperplastic red marrow in response to conditions that stimulate increased hematopoiesis. These include chronic hemolytic anemia, hematopoietic growth factor treatment, cyanotic congenital heart disease, participation in endurance sports, and dwelling at high altitude. Marrow reconversion occurs anatomically in the reverse order of normal marrow conversion.

In thalassemia and sickle cell disease, the appearance of the marrow on MRI reflects the combined effects of red marrow hyperplasia, iron deposition, iron chelation therapy, and, in the case of sickle cell disease, medullary bone infarcts. The MRI appearance of acute medullary bone infarction in sickle cell disease can be indistinguishable from acute osteomyelitis, and include marrow edema, periostitis, extra-osseous soft tissue edema, and fluid collections [7,8,9].

Gaucher disease results from mutations that confer a deficient level of activity of β-
glucocerebrosidase, leading to accumulation of glucocerebroside in the lysosomes of macrophage-like cells termed Gaucher cells. Gaucher cells initially infiltrate marrow of the lumbar spine, followed by the extremities, and produce low signal intensity of the marrow on T1-weighted sequences. High signal intensity foci on fat-suppressed T2-weighted or STIR sequences may represent complicating infarction or osteomyelitis. A practical approach for MRI evaluation of the skeleton in Gaucher disease is to image the lumbar spine and/or the lower extremities with CSE T1-weighted sequences, supplemented by fat-suppressed FSE T2-weighted or STIR sequences for the detection of complications. Although MRI quantitative chemical shift imaging (QCSI) is the most sensitive method for assessing bone marrow infiltration, it is technically demanding and semi-quantitative MRI methods such as bone marrow burden (BMB) scoring are preferred in routine clinical practice. MRI has been advocated to monitor for an increase in the fat fraction of the marrow as an indicator of response to enzyme replacement therapy. However, the normal abundance of hematopoietic marrow in young children creates difficulty in detecting and quantifying the extent of Gaucher cell infiltration by MRI, and the normal developmental conversion of hematopoietic to fatty marrow can be misinterpreted as response to treatment [10,11].

Leukemia typically manifests as widespread decreased marrow signal intensity on T1-weighted sequences and increased signal intensity on fat-suppressed T2-weighted and STIR sequences. The infiltration is often diffuse, including involvement of the epiphyses. The findings are less conspicuous in hematopoietic marrow than fatty marrow and consequently are more difficult to appreciate in younger children in whom marrow conversion has not yet occurred. The MRI appearance of leukemia can be mimicked by diffuse infiltration of the marrow by metastatic disease, myelodysplastic or myeloproliferative syndromes, or conditions associated with hematopoietic marrow hyperplasia. MRI is useful in detecting cases of so-called “aleukemic” or “subleukemic” leukemia that present with a normal or low white blood cell count and no blasts on peripheral blood smear, and may masquerade clinically as aplastic anemia, osteomyelitis, or juvenile rheumatoid arthritis for several months. Many of these patients have nonspecific bone or joint pain and undergo musculoskeletal MRI exams that reveal bone marrow infiltration and prompt the correct diagnosis of leukemia. Relapsed leukemia can been detected by MRI in some instances several weeks before it is diagnosed by iliac bone marrow aspirate or biopsy, due to iliac marrow sampling bias and earlier relapse in the vertebral marrow than in the iliac crest marrow. However, regenerating hematopoietic marrow can be indistinguishable from residual or recurrent leukemic marrow infiltration on MRI, underscoring the limited specificity of MRI in evaluation of the marrow [12,13,14].

Marrow involvement by lymphoma in children is most strongly associated with Burkitt lymphoma, lymphoblastic lymphoma, and lymphocyte-depleted Hodgkin disease. The pattern of involvement is usually multifocal, with a predilection for sites of predominantly hematopoietic marrow. When involvement is diffuse, an arbitrary threshold of neoplastic lymphoid cells constituting 25% or greater of the marrow cellularity differentiates the diagnosis of lymphoblastic leukemia from lymphoma. Although MRI is not part of the routine evaluation of
the bone marrow in pediatric lymphoma patients, MRI is more sensitive than Tc-99m phosphonate bone scintigraphy for the detection of marrow involvement by lymphoma [14,15].

Metastatic involvement of the marrow is more difficult to detect by MRI in hematopoietic marrow than in fatty marrow. Compared to osteomyelitis or other inflammatory conditions, metastases are usually better-defined with less edema of the marrow and extra-osseous soft tissues. Metastatic disease of the marrow tends to be multifocal, but can be diffuse, most commonly in neuroblastoma. In children and adolescents with solid tumors, whole-body MRI is superior to technetium-99m phosphonate bone scintigraphy for the detection of bone marrow metastases, particularly in the spine, pelvis, and extremities. Whole-body MRI also identifies additional bone marrow lesions in Langerhans cell histiocytosis compared to radiographic skeletal survey or bone scintigraphy. MRI is more sensitive but less specific than MIBG scintigraphy for infiltration of the marrow by neuroblastoma. Due to the effects of tumor treatment on the marrow, MRI is of limited utility for assessing residual metastatic disease in the marrow [16,17,18].

In untreated aplastic anemia, the signal intensity of the bone marrow on MRI sequences in untreated aplastic anemia approaches that of subcutaneous fat, reflecting the paucity of hematopoietic marrow. This is easiest to appreciate in regions that normally have a relatively greater abundance of hematopoietic marrow, such as the axial skeleton and pelvis, and may be indistinguishable from normal fatty marrow in other regions of the skeleton. Loss of high marrow signal intensity on T1-weighted sequences in aplastic anemia patient suggests transfusional hemosiderosis, regenerative hematopoietic marrow, or development of myelodysplastic syndrome or leukemia [19,20].

Bone marrow infarction is associated with a number of conditions, including sickle cell disease, Gaucher disease, chronic renal failure, bone marrow transplantation, pancreatitis, steroid therapy, and antiretroviral therapy for HIV infection. Bone marrow infarction is unusual in hematopoietic marrow, except in patients with hemoglobinopathies. The infarction often has a geographic shape with a serpiginous margin of low signal intensity on T1-weighted sequences. T2-weighted sequences may demonstrate a characteristic “double line sign” consisting of an outer low signal intensity rim corresponding to sclerotic bone and an inner rim of high signal intensity corresponding to vascularized granulation tissue or chondroid metaplasia. Areas of low signal intensity on both T1-weighted and T2-weighted sequences in mature infarcts represent fibrosis or calcification. Intense contrast enhancement is commonly seen at the periphery of evolving infarcts, and dynamic contrast-enhanced MRI has been touted for early diagnosis, although the diagnosis can usually be confidently made on conventional MRI sequences without intravenous contrast [21,22].

Therapy with hematopoietic growth factors (e.g., G-CSF, GM-CSF, erythropoietin) induces hematopoietic marrow hyperplasia and reconversion that exhibits low signal intensity on T1-weighted sequences. The peak of hematopoietic marrow hyperplasia observed by MRI occurs about two weeks after discontinuation of G-CSF administration, and the bone marrow alterations normalize in most patients within six weeks after discontinuation of treatment. The marrow changes can be diffuse or patchy and asymmetric, and simulate bone marrow involvement by
leukemia, metastatic disease, or other infiltrative process. The changes can also obscure marrow lesions [23].

Bone marrow in the field of radiation therapy undergoes edema and hemorrhage in the acute phase, followed by replacement of hematopoietic marrow by fat and fibrosis in the chronic phase. The effects of radiation therapy on the marrow are sharply delimited by the radiation portal, and are more conspicuous in locations previously occupied by hematopoietic marrow, particularly the vertebrae and pelvis. For doses < 30-40 Gy, fatty replacement of the marrow is incomplete and hematopoietic marrow regeneration can occur [24].

Iron overload of the marrow is most commonly a consequence of numerous blood transfusions for anemia. Iron overload reduces the signal intensity of the marrow, particularly on T2*-weighted gradient echo sequences, but also on T2-weighted spin echo sequences, and, at high iron concentrations, on T1-weighted spin echo sequences. Iron overload can also cause a reduction in signal intensity of other components of the reticuloendothelial system, such as the spleen and liver. The MRI findings of marrow iron overload regress with iron chelation therapy or cessation of transfusions [8,25].

Sources of erroneous interpretations of a bone marrow disorder on pediatric MRI exams include spurious alterations in the marrow signal intensity from volume averaging of the marrow with the bony cortex or cartilage and ignorance of the normal pattern of marrow conversion and physiologic alterations in bone marrow signal intensity. Patchy foci of high signal intensity on T2-weighted and STIR sequences are commonly seen in the marrow of the tarsal bones in asymptomatic children. These do not persist beyond adolescence, are typically bilateral and mostly symmetric, and are possibly attributable to residual hematopoietic marrow, minor contusions or response to alterations in weight-bearing during growth and development [26,27].

In many areas of the world, community-acquired methicillin-resistant Staphylococcus aureus (CA-MRSA) is emerging as a leading cause of serious musculoskeletal infections affecting otherwise healthy infants, children and adolescents. Deaths from CA-MRSA may now exceed or soon exceed deaths from AIDS in the United States [28]. Spread of CA-MRSA is facilitated by close skin-to-skin contact, skin cuts or abrasions, sharing of contaminated surfaces and items, crowded living conditions, and poor hygiene. In 90-95% of cases, the infection involves the skin or superficial soft tissues (“spider bite”, pustules, carbuncle, furuncle, cellulitis), while in 5-10% of cases, invasive disease involving the musculoskeletal system as osteomyelitis, septic arthritis, pyomyositis, or fasciitis occurs. Infants are at higher risk of invasive disease compared to older children. Invasive disease is rare if the C-reactive protein (CRP) level is normal, while a markedly elevated CRP level and CA-MRSA strains expressing the Panton-Valentine leukocidin correlate with the presence of invasive disease and abscesses. Management of invasive CA-MRSA entails antibiotics, aspiration of infected fluid or tissue for culture and sensitivity testing, and prompt abscess drainage. Urgent MRI is indicated to delineate disease extent and fluid collections if invasive disease is suspected [29,30].

On MRI, osteomyelitis classically manifests as ill-defined marrow edema with or without associated periostitis and bone destruction. Intramedullary suppuration or marrow necrosis is very common in CA-MRSA osteomyelitis and appears as non-enhancing foci in the marrow on
CA-MRSA readily breaches tissues barriers, and subperiosteal, intramuscular, or subcutaneous abscesses are not uncommon at the time of presentation with osteomyelitis. Over 90% of cases of severe invasive CA-MRSA infections with sepsis and hypoperfusion are associated with osteomyelitis, septic arthritis, or pyomyositis, often multifocal. Approximately 30% of cases of severe invasive CA-MRSA infections are associated with deep venous thromboses near the sites of osteomyelitis, and septic pulmonary emboli are often present in fatal cases [31].

Conventional practice has been to perform bone scintigraphy for cases of suspected osteomyelitis in children with negative radiographs, with MRI reserved for suspected spinal or pelvic osteomyelitis or slow responders to treatment [32,33]. However, MRI is preferred over bone scintigraphy as the primary imaging modality for osteomyelitis in locales where CA-MRSA is endemic, due to the high frequency of extra-osseous complications such as abscesses and deep venous thromboses amenable to diagnosis with MRI but not bone scintigraphy, and the high frequency of osteomyelitis that is occult or “cold” on bone scintigraphy, related to regional ischemia, vascular thrombosis, intraosseous abscess/necrosis, or isolated growth cartilage involvement. While osteomyelitis typically involves the metaphyses in children and adolescents, the metaphyseal vessels traverse the physes to supply the vascular sinusoids of the epiphyses and apophyses in infants, providing a basis for the proclivity for epimetaphyseal involvement and subsequent skeletal growth disturbances from osteomyelitis in infants. Infection of the unossified epiphyses and apophyses in infants may be occult not only on bone scintigraphy, but also on conventional MRI sequences without contrast. The normal growth cartilage of the epiphyses and apophyses in infants has prominent vascularity, and infectious chondritis manifests as diminished cartilage enhancement on post-contrast MRI sequences. It is important to survey a large field-of-view of the extremities in cases of suspected osteomyelitis in infants due to the frequent multifocal nature and the difficulty in localizing the site of infection by clinical exam [29].

In addition to osteomyelitis, septic arthritis is common with invasive CA-MRSA infections. A delay in diagnosis of septic arthritis increases the risk of articular cartilage destruction, osteonecrosis, growth deformity, and sepsis. Even if septic arthritis alone is suspected, some pediatric orthopedists in CA-MRSA endemic areas are willing to defer joint ultrasound or arthrocentesis if prompt MRI is available to define other drainable fluid collections prior to surgery. The differential diagnosis of septic arthritis includes not only osteomyelitis and pyomyositis, but non-infectious inflammatory disorders such as transient synovitis and juvenile rheumatoid arthritis. Transient synovitis is the most common cause of acute hip pain in children 3-10 years of age, and is associated with a recent history of an upper respiratory infection in one-half of cases. The presence of a high fever and elevated ESR, CRP, or white blood cell count favors septic arthritis over transient synovitis, while the joint effusion size is not a useful discriminator. MRI may be useful in clinically equivocal cases, since synovial thickening, juxta-articular soft tissue edema, and decreased femoral capital epiphysis enhancement are more commonly seen in septic arthritis, bilateral joint effusions are more commonly seen in transient synovitis, and bone marrow signal intensity alterations are not seen in transient synovitis [34,35].
The emergence of CA-MRSA has led to a greatly increased incidence of pyomyositis in children. CA-MRSA pyomyositis is accompanied by osteomyelitis or septic arthritis in 66% of cases and is preceded by skin barrier penetration (e.g., bug bite, excoriation, laceration) in 50% and by trauma or vigorous activity in 25%. HIV infection and diabetes are not risk factors in children, unlike in adults. Pyomyositis is most common of the musculature of the lower extremity and pelvis, and appears as high signal intensity of the musculature on T2-weighted and STIR sequences. Gadolinium-enhanced T1-weighted sequences are valuable for defining non-enhancing foci representing intramuscular abscesses or myonecrosis. Isolated pyomyositis of the piriformis muscle is increasingly recognized and characteristically presents with intolerance to sitting, avoidance of walking due to exacerbation of pain by hip internal rotation and adduction, and imprecise lower extremity pain mimicking sciatica due to the proximity of the piriformis muscle to the sciatic nerve and sacral plexus [36,37].

Conditions other than pyomyositis that can show extensive abnormal hyperintensity of muscle on T2-weighted and STIR sequences include idiopathic inflammatory myopathies (such as dermatomyositis) and rhabdomyolysis (which can be distinguished by markedly elevated creatine kinase levels), neoplastic infiltration (such as non-Hodgkin lymphoma) and subacute or chronic denervation. Rhabdomyolysis most commonly involves the thigh, buttock, paraspinous, and pelvic musculature. Viral myositis causes the vast majority of cases of rhabdomyolysis in childhood, while trauma, exercise and drug-related causes peak in adolescence. The classic triad of myalgia, dark urine, and weakness for the clinical diagnosis of rhabdomyolysis in adults is present in < 1% of cases of childhood rhabdomyolysis, and the diagnosis of rhabdomyolysis in children is occasionally first suggested on the basis of the findings noted on MRI [38,39].

The clinical and imaging presentation of musculoskeletal infections in children can be simulated by certain neoplasms. For example, fever, elevated ESR levels, and bone marrow edema, bone destruction, and periostitis are common in Langerhans cell histiocytosis and Ewing’s tumor. However, the peripheral margins of tumors in the bone marrow tend to be sharper defined than in osteomyelitis, and a diaphyseal location or enhancing extraosseous soft tissue mass are much more common with tumor than with osteomyelitis. The clinical and imaging findings of chronic recurrent multifocal osteomyelitis (CRMO) can mimic infection or malignancy. CRMO most frequently occurs in children and adolescents, and most commonly affects the long bone metaphyses (especially the tibia), spine, pelvis, and sternocostoclavicular regions. Bone involvement is often multifocal and sometimes symmetric, and the clinical course is typically protracted with recurrences. Unlike acute bacterial osteomyelitis, bone biopsy in CRMO is usually sterile with nonspecific inflammation and a predominance of plasma cells, and no abscess, fistula, or sequestrum is observed on imaging [40].

References:


Pre-Test Questions

1. Which of the following conditions is not typically associated with abnormal low signal intensity of the bone marrow of children on non-enhanced conventional spin echo T1-weighted sequences?
   a. Leukemia
   b. Chronic hemolytic anemia
   c. Metastatic infiltration by neuroblastoma
   d. Aplastic anemia
   e. G-CSF therapy

2. Which of the following statements regarding invasive musculoskeletal infections from community-acquired methicillin-resistant Staphylococcus aureus (CA-MRSA) in children is false?
   a. Infants are at higher risk than older children than adults
   b. Deep venous thrombosis tend to occur near the site of osteomyelitis
   c. Subperiosteal and intramuscular abscesses are common
   d. Infectious chondritis occult on bone scintigraphy is detectable by MRI
   e. Infants are prone to diaphyseal osteomyelitis