**MSK Tumors and Marrow Evaluation**

**Bone Marrow**

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(i) **Introduction**

Bone marrow consists of trabecular bone and a variety of cells including hematopoetic, fat, stroma and reticuloendothelial system cells as well as sinusoids. The weight of the bone marrow is approximately 5% of the whole body weight. Bone marrow composition changes with age, which is reflected in a change in signal characteristics in MR images. Red marrow, which is found in younger individuals is composed of approximately 40% fat and 40% water, while yellow bone marrow contains approximately 80% fat and 15% water. MRI is a very sensitive technique to assess physiological changes in bone marrow composition and to detect bone marrow abnormalities. Intimate knowledge of age-related morphology as well as reactive physiological changes is required to evaluate bone marrow pathology.

(ii) **Standard Techniques**

Standard MR sequences for bone marrow pathology include T1-weighted fast spin-echo (FSE), STIR (short T1 inversion recovery) and T2-weighted fat saturated FSE sequences. T1-weighted sequences are very useful for initial evaluation as signal of muscle and intervertebral disc may be applied for internal calibration: bone marrow that is lower in signal than muscle and disc is considered as abnormal (1). Fluid sensitive sequences should be used with fat saturation to better visualize bone marrow pathology; accordingly STIR and T2-weighted fat saturated FSE sequences are recommended. Contrast enhanced sequences may add information, for example in better assessing intraspinal pathology or soft tissue extension of lesions, but application is discussed controversially. Important applications of Gd-based contrast media include (1) differentiation of cystic and solid bone marrow lesion, (2) differentiation of viable and necrotic tissue to guide biopsy, (3) abscess versus solid tissue in infection and (4) monitoring of therapy response in tumor and infection. MR techniques have evolved substantially and extensive coverage of the skeleton is possible with good image quality and within a reasonable acquisition time. Whole body MR imaging techniques are popular, in particular in Europe, and different techniques have been described, which include whole body coils (2, 3).
Normal Bone Marrow

In evaluating MR images one has to be aware of age-related changes in signal characteristics: in young patients substantial amounts of hematopoietic bone marrow are found and below the age of 10 years in T1-weighted images the bone marrow may be lower in signal intensity than surrounding muscle or intervertebral disc (4) (Figure 1). Above the age of 10 years lower signal intensity is considered as abnormal. Conversion from hematopoietic to fatty bone marrow starts in the periphery and the distal part of the long bones. By the age of 20 years most of the appendicular skeleton contains fatty bone marrow, while the central skeleton including proximal femur and humerus contain largely hematopoietic bone marrow.

In the 6th decade of life a substantial amount of fatty bone marrow is also found in the axial skeleton. In older patients bone marrow of the axial skeleton may be heterogenous on MRI due to atrophy and degeneration of the bone marrow, which should not be confused with diffuse neoplastic infiltration of bone marrow. Also note that reconversion of fatty to hematopoietic bone marrow may be observed, associated for example with status post chemotherapy and GCSF therapy, obesity, pulmonal pathology, smoking and marathon running.

Hematopoietic bone marrow is an important MRI differential diagnosis in myeloproliferative disorders and sometime is very difficult to differentiate from neoplastic disease in patients with malignancies. However, in MR images hematopoietic bone marrow is usually not geographic and more vague in appearance, it is frequently symmetric and located in the metaphyses, the signal is brighter than that of muscle in T1-weighted sequences. Bone marrow metastases are frequently more focal and rarely diffuse. FDG-PET is not helpful in differentiating diffuse neoplastic bone marrow disease and hematopoietic bone marrow as both are frequently associated with increased tracer uptake.

Abnormal Bone Marrow

1. Neoplastic disease
   1.1. Myeloproliferative disorders
   Myeloproliferative disorders are a group of diseases that cause an overproduction of bone marrow cells such as platelets, white blood cells, and red blood cells. These include myelofibrosis, polycythemia vera, chronic and acute leukemias and primary thrombocythemia. Multiple myeloma is the most common neoplastic disease of the bone marrow.

   Predominantly fibrotic bone marrow pathology
   In myelofibrosis polyclonal activation of fibroblasts occurs, which secrete collagen, causing bone marrow fibrosis. This results in extramedullary hematopoiesis in liver and spleen and immature blood cells in the peripheral blood. MRI is very sensitive in assessing the extent of the disease; low signal intensity changes both in T1- and T2-
weighted images are shown, due to replacement of marrow fat by collagen and reticulin fibers. Note however, that these signal changes may also be found in children with leukemia and Gaucher’s disease as well as in iron overload (chronic hemolysis, thalassemia) and AIDS (5).

**Predominantly hypercellular bone marrow pathology**

Acute myelogenous leukemia (AML) is the most frequent leukemia found in adulthood and has a number of different subtypes. Auer rods and discrete tumor masses infiltrating the soft tissues are typical findings. Acute lymphoblastic leukemia (ALL) is the most common childhood malignancy; B-cell, T-cell and null cell ALL are differentiated, B-cell ALL has a better prognosis. Infiltration of the bone marrow may be diffuse or focal, typically T2 bright and T1 low in signal. After therapy, however, signal may also be low in T2-weighted images.

Multiple myeloma (MM) is a clonal B-lymphocyte neoplasm and the most frequent primary malignancy of the bone marrow, accounting for 10% of hematologic malignancies. It is usually systemic, but solitary osseous myeloma is found in approximately 5% of the cases and frequently these tumors progress to MM. Amyloidosis and light-chain cast nephropathy are additional characteristic findings. Histologically sheets of plasma cells are found in the bone marrow.

There are three pathological MR patterns in MM:

(i) A focal pattern with localized areas of abnormal marrow is most frequent. These focal lesions are low in signal in T1-weighted images, bright in fat-saturated T2-weighted images and show contrast enhancement. This pattern is found in multiple myeloma and lymphoma, but is also typical for metastatic disease from solid primary malignancies.

(ii) The diffuse pattern shows replacement of the normal marrow with intervertebral discs and muscle appearing in T1-weighted sequences similar or higher in signal than the bone marrow. The bone marrow is bright in fat saturated T2-weighted or STIR sequences and shows substantial contrast enhancement. Depending on the degree of diffuse bone marrow infiltration, however, diagnosis may be difficult and if less than 20% of the bone marrow is diffusely infiltrated it is not possible to differentiate malignant infiltration with confidence from hematopoietic bone marrow (6). The diffuse pattern of disease is found in MM, acute leukemias and other myeloproliferative diseases. (iii) The variegated pattern consists of multiple, innumerable, small foci of disease on a background of normal bone marrow. These foci are low in signal intensity in T1-weighted images, bright in T2-weighted images and enhance after contrast administration.

![Fig. 2: Focal pattern of multiple myeloma. Axial T1-weighted image of the pelvis shows focal lesions in the right sacrum and ilium.](image-url)
After treatment bone marrow changes may resolve, but may also be unchanged, even if patients achieve complete remission. Sometimes changes in the enhancement pattern may be shown or transformation of a diffuse into variegated or focal pattern may be found (7). Progression of vertebral compression fractures also does not necessarily suggest disease progression but may be due to collapse of the unsupported vertebra.

1.2. Lymphoproliferative disorders
These disease entities are divided into Hodgkin’s and non-Hodgkin’s lymphomas and infiltration of the bone marrow is found in 5-15% of patients with Hodgkin’s and 20-40% of patients with non-Hodgkin’s disease (7). MRI may show the infiltration more sensitively than bone marrow scintigraphy but may be less accurate than FDG PET in assessing therapy response. On T1-weighted MR images involvement is usually more diffuse or heterogeneous and less frequently focal. These MR findings are not typical for this disease entity and may be found in myeloproliferative disease too. A soft tissue mass around an apparent intact cortical bone, however, raises concern for lymphoma, though it may be found in small cell malignancies too.

1.3. Secondary neoplasias
Metastases are the most frequent malignancies in the bone marrow and usually they are focal, less frequently diffuse. Whole body MRI is very sensitive in detecting these lesions, and has a superior sensitivity compared to bone and bone marrow scintigraphy (8, 9). T1-weighted FSE or STIR sequences usually are well suited for bone marrow imaging in patients with suspected metastases. One of the most challenging differential diagnoses in pathologic compression fractures are insufficiency fractures due to osteoporosis. In patients with osteoporotic compression fractures the bone marrow signal may be normal, if fractures are old, in subacute and acute fracture the bone marrow signal is abnormal but usually extends parallel to the endplate and does not involve the whole vertebra. The posterior border of fractured vertebrae in osteoporosis is usually concave and not convex and signal abnormalities do not typically extend into the pedicles.

2. Metabolic and bone marrow storage diseases

Gaucher’s disease is a metabolic storage disorder due a defect of the enzyme glucocerebrosidase. This leads to progressive proliferation of Gaucher cells with accumulated undegraded glycolipids, resulting in expansion of the marrow space (Erlenmeyer flask deformity), bone erosion with an increased number of fractures and infarction of the bone marrow. The Gaucher cells have low signal intensity both in T1- and T2-weighted sequences (Fig. 3). Bone marrow infiltration starts proximal and increasingly affects more peripheral areas of the appendicular skeleton.
Bone marrow infarction is also a typical finding related to Gaucher’s disease and is characterized by a more serpiginous pattern with bright signal in fat saturated T2-weighted or STIR sequences. Secondary hemochromatosis may be due to repeated blood transfusions and leads to diffusely low signal intensity of the bone marrow in both T1- and T2-weighted sequences. Please note that primary hemochromatosis usually does not affect MR morphology of bone marrow.

3. Hemoglobinopathies
Sickle cell disease is found in approximately 0.15% of African-American children and leads to small vessel occlusion and hemolytic anemia in particular with decreased oxygen tension. In the bone marrow an increased amount of hematopoietic cells is demonstrated and bone marrow infarction is a typical finding. The increased amount of red bone marrow goes along with diffusely low signal intensity lesions in the T1-weighted sequences and increased signal in STIR sequences. Bone marrow infarction has more complex signal changes due to necrosis, fatty degeneration and granulation tissue.
In thalassemia a defect of hemoglobin subunits is found leading to anemia. This anemia causes an increase in hematopoietic bone marrow, which sometimes can cause substantial expansion of bone marrow space and tumor-like extramedullary hematopoiesis.

4. Bone marrow edema pattern around joints
Bone marrow edema pattern is found in a number of inflammatory and degenerative joint diseases and is associated with different histological abnormalities such as osteonecrosis, bone marrow fibrosis, bone remodeling and fibrovascular tissue ingrowth (10, 11). Bone marrow edema in osteoarthritis has been also associated with increasing amounts of joint pain and more progressive disease in inflammatory arthropathies. Transient osteoporosis is characterized by extensive bone marrow edema pattern without focal abnormalities and typically affects the proximal femur in middle-aged men and women in the third trimester of pregnancy. The etiology is not well understood and trauma was associated with this disease; transient osteoporosis follows a typical disease course and is completely reversible in 3-9 months.
Avascular necrosis is typically not associated with large amounts of bone marrow edema pattern in the early phases; larger amounts of bone marrow edema pattern are seen, however, in later stages of the disease.
5. **Insufficiency fractures**

Focal bone marrow edema pattern at the distal femur of the knee joint and the proximal femur of the hip joint with linear, subchondral signal abnormalities in older individuals is typical for insufficiency fractures (Fig. 4). This disease entity received significant attention recently and was previously termed frequently as osteonecrosis. Insufficiency fractures at these sites usually lead to accelerated osteoarthritis. At the knee subchondral insufficiency fractures may be associated with meniscus abnormalities and previous meniscus resection. Insufficiency fractures are also frequently found at the pelvis in patients with osteoporosis and are not infrequently misinterpreted as bone metastases.

**(vi) Advanced techniques**

To better differentiate neoplastic and osteoporotic fractures diffusion imaging has been introduced and a large number of studies have been performed demonstrating the benefit of these sequences (12, 13). Evaluations of bone marrow perfusion with standard small molecular contrast agents and, more recently, with macromolecular contrast agents are currently being applied for therapy monitoring, differentiate hematopoietic and neoplastic bone marrow as well as to assess bone marrow viability. Cell-specific contrast agents are expected to improve the sensitivity and specificity of bone marrow MR imaging (14). Bone marrow spectroscopy has shown benefit to better evaluate metabolic bone disease (15).

**(vii) Conclusion**

Imaging characteristics of normal bone marrow change through life and familiarity with these changes is important to correctly approach bone marrow abnormalities. Neoplastic disease of the bone marrow is a frequent pathology and the individual diseases entities may have different morphologic patterns. Storage diseases and hemoglobinopathies also have typical bone marrow patterns, which are well visualized with MRI but may occasionally be difficult to differentiate from neoplastic disease. Recently bone marrow edema pattern associated with degenerative and inflammatory arthropathies was extensively studies as it may have clinical and prognostic implications. Insufficiency fractures are frequently found in the older population and are typically associated with extensive bone marrow signal abnormalities. While standard imaging of bone marrow is based on a few standard sequences (in particular T1- and fs T2-weighted FSE as well as STIR sequences) new techniques are being developed to better characterize certain pathologic conditions.
References: