Imaging of musculoskeletal complications following hematopoietic stem cell transplantation in children

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Learning objectives

The aim of this paper is to present and describe imaging findings for musculoskeletal complications after HSCT in children.
Background

The transplantation of allogeneic or autologous hematopoietic stem cells is an established curative treatment for hematological malignancies, including leukemia and lymphoma, and plays an important role in the management of bone marrow failure, hemoglobinopathies, congenital immunodeficiencies, metabolic diseases, genetic disorders and solid tumors [1]. Knowledge regarding the stages of hematopoietic stem cell transplantation (HSCT) is important for understanding complications associated with this procedure. HSCT includes the pre-transplantation, transplantation and post-transplantation periods. The pre-transplantation period (4-6 days prior to transplantation) is referred to as conditioning; during this time, chemotherapy or total body irradiation (TBI) is administered to eradicate tumor cells. During transplantation, donor stem cells are infused intravenously and migrate through the bloodstream to marrow spaces. The post-transplantation period can be divided into engraftment (first 15-30 days) which stem cells grow in the marrow spaces, early post-engraftment period (from 15 to 30 days to 100 days after transplantation) and late post-engraftment period (more than 100 days after transplantation). During engraftment, there is severe marrow aplasia with pancytopenia [2]. The timing of complications that occur after transplantation may be described with reference to three periods: the pre-engraftment period, the early post-engraftment period and the late post-engraftment period. Early post-engraftment complications include infections, acute graft versus host disease (GVHD) and graft failure. Late post-engraftment complications include recurrence of the primary disease, chronic GVHD, osteonecrosis and secondary malignancies.

Musculoskeletal complications are primarily associated with TBI in preparation for transplantation, the prolonged use of steroids to treat GVHD, chronic GVHD [3,4].

Although radiographs are often initially obtained to evaluate musculoskeletal complications, especially in cases involving possible osteonecrosis, magnetic resonance imaging (MRI) is more sensitive, particularly during the early stages of disease [4].
Findings and procedure details

Changes in bone mineral density (BMD)

Decreased BMD after HSCT occurs secondary to endocrine dysfunction, irradiation, corticosteroids, and chronic GVHD, predisposes patients to pathologic fractures [5,6]. Osteopenia and osteoporosis typically remain asymptomatic until insufficiency fractures occur. In children, World Health Organization (WHO) criteria are used to clinically diagnose osteopenia (z = -1 to -2.5) and osteoporosis (z < -2.5) based on z-scores calculated from age-, sex-, and race-matched reference data [5] (figure 1). The method employed to measure BMD in children is dual energy X-ray absorption (DEXA). Early detection of diminished BMD will allow for appropriate interventions and may prevent future disability. Relative to DEXA, radiography provides less quantitative assessments of bone density with increased lucency and cortical thinning and for pediatric patients, osteoporosis is easily overestimated using radiographs (figure 2).

Bone infarction

Bone infarction, which is known as osteonecrosis or avascular necrosis, is a common complication after HSCT, particularly in weight-bearing joints such as hips, knees and ankles. Plain radiographs have poor sensitivity for detecting bone infarction prior to subchondral collapse, whereas MRI can detect osteonecrosis during early stages, when this condition remains asymptomatic (figure 3). Osteonecrosis has characteristic findings on MRI, including geographical areas with dark serpiginous borders that are within hyperintense marrow on coronal non-enhanced T1-weighted images but bright on T2-weighted or short-tau inversion recovery (STIR) images (figure 4). Central areas within the border are hyperintense, similar to the surrounding marrow on T1-W and lose signal compared to surrounding marrow on fat-saturated T2-W or STIR image (figures 5 and 6). Contrast enhancement of the border reveals inflammation and hyperemia (figure 5). Additional sagittal imaging of the articular surface is sufficient for the detection of osteochondral lesions and collapse [2,3,4,7] (figure 7).

Stress injuries

Stress injuries of the bone are classified as fatigue fractures (which are also known as stress fractures) or insufficiency fractures, depending on the state of the underlying bone. Fatigue fractures occur when a normal bone is injured by abnormal activity, whereas insufficiency fractures occur when abnormal bone is subjected to ordinary stress [8,9,10,11]. The physis and the apophysis, which are among the weaker parts of the musculoskeletal system in children, are common sites for stress injuries (figure 8). Abnormal stresses at these sites may result in the disruption of endochondral ossification, ultimately resulting in physeal widening, and repetitive microtrauma also leads to bony cortical defects and stress injuries [9] (figure 9).
Plain radiography is an initial method for confirming stress injuries, although this approach produces a high rate of false negatives for such insufficiency fractures [11]. While lacking in sensitivity early in the disease, radiographs will classically show linear sclerosis, periosteal elevation, and cortical thickening, consistent with healing [9].

MR imaging is currently the best diagnostic modality for stress injuries. Marrow edema results in low signal intensity on T1-weighted and high signal intensity on STIR and T2-weighted MR images. In contrast, a fracture line is well defined and linear and is depicted as low signal intensity on T1- and T2-weighted MR images (figures 6). Subperiosteal fluid is a helpful ancillary finding in subtle insufficiency fractures. When intravenous contrast agents are administered, the medullary space shows enhancement secondary to edema [8] (figure 7). Radionuclide scanning is sensitive but lacks the specificity to differentiate marrow changes of stress injuries from tumors and infection [8].

Scoliosis

Effect of radiotherapy is alteration in axial alignment, often presenting long after treatment as scoliosis or kyphosis [13]. Chances of spinal malalignment increase with younger age at exposure, higher doses, and asymmetrical radiation. Bony hypoplasia, especially involving flat bones, can result from inhibition of osteogenesis by radiation. Scoliosis is a rare bone growth deformity observed after HSCT is performed in pediatric patients and is thought to be caused by radiation-induced asymmetrical growth plate impairment [1,12]. Radiographs play an important role in assessing bone growth and could be sufficient for such assessments in most cases [12] (figure 10).

Myositis, fasciitis and arthritis

Musculoskeletal manifestations of chronic GVHD in children include joint contractures, polymyositis, polyserositis, fasciitis and arthritis [14,15,18]. Functional limitations from joint contractures, arthralgias and fatigue can be severe [14]. Chronic GVHD diagnostic guidelines proposed fasciitis as diagnostic, and myositis as a distinctive sign and symptom of chronic GVHD [15]. Myositis, fasciitis and arthritis are relatively rare manifestations of chronic GVHD, and MRI is the diagnostic imaging modality for these conditions [16,17,18]. In children with myositis, MRI is often used both to establish the diagnosis and to monitor disease activity. Myositis and fasciitis result in high signal intensity in muscle and along fascia in fat-suppressed T2-weighted and STIR images [16,17] (figures 11 and 12). Arthritis is uncommon, occasionally associated with the presence of antibodies and result in synovial thickening, enhancement and effusion on MRI [11]. Repeated bone marrow biopsies and stem cell aspiration from iliac bone may cause focal abnormalities (figure 13).
Fig. 1: Osteoporosis in a 12 year old boy 435 days after HSCT for myeloid leukemia. DEXA image (A) of proximal femur show femoral neck, Ward area and trochanter. Values obtained from graphic (B) and table (not shown) are total BMD = 0.605 g/cm² and z score= -2.8.

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**Fig. 2:** AP left hand radiograph shows increased lucency and cortical thinning in a 9 year old girl 696 days after HSCT for Beta Thalassemia. Hand radiograph also shows bone age of 6 years.

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Fig. 3: Avascular necrosis in a 15 year-old girl with aplastic anemia 51 days after HSCT. AP pelvis radiograph (A) shows normal right hip (blue arrow) and coxa plana of left hip (white arrow). Coronal STIR (B) and coronal non enhanced T1-weighted (C) images obtained on same day show mild osteonecrosis of right femur neck (yellow arrow). 250 days after HSCT, AP pelvis radiograph (D), coronal STIR (E) and coronal non enhanced T1-weighted (F) images show progression of osteonecrosis of femur neck (yellow arrow) with collapse and dislocation of right femur head (open blue arrow).

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Fig. 4: Bone infarcts in a 16 year old boy 245 days after HSCT for acute lymphoblastic leukemia. Coronal (A), sagittal (B) STIR and sagittal T1 weighted (C) images of the knees show distal femoral and proximal tibial geographic lesions (white arrows) characteristic of osteonecrosis.

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**Fig. 5:** Bone infarcts in a 13 year-old girl with aplastic anemia 221 day after HSCT. Sagittal STIR (A) and coronal non enhanced T1-weighted (B) images show multiple geographic areas of abnormal signal intensity in talus, calcaneus and distal tibia. Axial fat suppressed (fs) non enhanced (C) and axial fs contrast enhanced (D) images show synovitis and arthritis of ankle with thickening and enhancement of synovium (white arrow) and synovial effusion. Border enhancement and hyperintensity reflects inflammation and hyperemia (green stars).

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**Fig. 6:** Coronal STIR (A) and T1 weighted (B) images of the knees show distal femoral and proximal tibial multiple geographic lesions (pink stars) characteristic of osteonecrosis in a 14 year old boy 245 days after HSCT for acute lymphocytic leukemia. Insufficiency fracture (white arrow) of distal diaphysis of tibia with soft tissue edema and synovial effusion (blue star) are present.

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Fig. 7: Sagittal STIR images of right ankle (A) and left ankle (B) show bone infarcts (blue stars) of bilateral talus and left calcaneus in a 17 year old girl, 768 days after HSCT for acute lymphoblastic leukemia. Coronal STIR (C) and coronal T1 weighted (D) images of bilateral ankles show progression of osteonecrosis with flattening and collapse of talus dome 3 years after HSCT.

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Fig. 8: Insufficiency fracture in a 3 year old girl with Beta Thalassemia. Coronal (A), axial (B) fs contrast enhanced T1 weighted and sagittal T2 weighted (C) images 191 days after HSCT show subtle fracture line with peripheral bone marrow and soft tissue edema. AP cruris radiograph (D) 202 days after HSCT show healed fracture with sclerosis and mild callus formation.

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Fig. 9: Insufficiency fractures in a 10 year-old boy with thalassemia major on chronic immunosuppressive therapy after HSCT presenting with thigh pain. Coronal non enhanced T1-weighted (A) and coronal STIR (B) images show widening of bilateral distal femoral physis and horizontal sclerotic fracture lines. MR images also demonstrate red marrow hyperplasia and reconversion induced by chronic hemolytic anemia. Lateral radiograph (C) shows a linear bands of sclerosis through the distal femoral and proximal tibial diaphysis and mild periosteal reaction consistent with healing.

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Fig. 10: Scoliosis thought to be caused by radiation therapy for spinal involvement of primary disease after allogeneic HSCT for lymphoid leukemia in an 8 year-old girl. Coronal T2-weighted (A,B) images 3 years after HSCT show abnormal curvature of scoliosis. AP radiographs of pelvis show scoliosis, right femur head dislocation and left femur head avascular necrosis (C) 580 days after allogeneic HSCT, normal findings (D) 73 days after HSCT.

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**Fig. 11:** Polymyositis, fasciitis and synovitis in a 17 year-old girl with chronic GVHD 299 days after allogeneic HSCT for acute lymphoblastic leukemia and relaps non Hodgkin lymphoma. Coronal STIR MR image (A) shows myositis of pelvic muscles as marked high signal intensity (pink stars) and accompanied subtle insufficiency fracture of right femur neck (pink arrow). Sagittal T2 fs images (B, C) show strong signal increase of paravertebral muscles consistent with myositis (pink stars). Coronal and axial STIR images (D) obtained 3 months later show myositis of pelvic floor muscles (pink stars) and prominent insufficiency fracture (pink arrow) of right femur neck. Axial fs T1-weighted non enhanced and enhanced (E) MR images show thickening, contrast enhancement (blue arrow) of synovium and synovial effusion (yellow star) consistent with synovitis and arthritis.
Fig. 12: Polimyositis, fasciitis and subcutaneous fat tissue edema in a 15 years old boy who underwent HSCT for lymphoid leukemia. Sagittal STIR (A) and axial STIR (B) images show signal increase of thigh muscles (pink stars), marked thickening of muscular fascia (white arrow), and signal increase of subcutaneous fat tissue (blue stars). Coronal and axial STIR images show medullary bone infarcts in the proximal diaphysis of bilateral femur (green stars).

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Fig. 13: Mild right parailiac edema and effusion secondary to bone marrow biopsy in a 7 years old boy 89 days after HSCT for Beta Thalassemia. Coronal STIR (A), T1- weighted (B) and axial T2 weighted (C) images show replacement of yellow marrow by hyperplastic red marrow consistent with increased hematopoiesis.

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Conclusion

In conclusion, with increase in long-term survival rates of childhood transplant recipients, musculoskeletal complications observed during the late post-engraftment period are important in order to prevent future disability. Familiarity with imaging findings of musculoskeletal complications and bone marrow involvement of the primary disease is important for appropriately diagnosing and treating pediatric HSCT recipients.
References

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