Skeletal manifestations of sickle cell disease: what the radiologist needs to know

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Learning objectives

- Review the pathology behind sickle cell disease (SCD), with particular reference to the skeletal manifestations of the disease.
- Outline the key skeletal manifestations of SCD, providing an illustrated review of their imaging appearances across a range of imaging modalities.
Background

SCD is a hereditary haemoglobinopathy which results in the production of abnormal haemoglobin and which can manifest with a variety of skeletal pathologies. SCD occurs due to an amino acid substitution within the beta globin gene in chromosome 11, leading to the production of defective haemoglobin (HbS). SCD occurs in individuals who are homozygous for HbS, whereas heterozygous individuals possess a sickle cell trait (these individuals typically rarely develop skeletal pathology).

The production of abnormal haemoglobin in SCD results in the formation of abnormal distorted red blood cells. These abnormal red blood cells can cause variable physiological disturbances including: [1] chronic anaemia, [2] immunosuppression, [3] abnormal blood flow, and [4] vaso-occlusion. It is a combination of these processes that underlies the skeletal pathologies associated with SCD; these include expansion of intramedullary haematopoietic marrow, bone infarction and avascular necrosis, and infections including septic arthritis and osteomyelitis. These pathologies occur throughout the skeleton, resulting in many different radiological appearances. Given that these presentations differ in their morbidity and treatment, an accurate diagnosis is necessary in order to direct appropriate management.
Imaging findings OR Procedure Details

As an institution with high rate of SCD in the local population, we have access to a rich source of imaging, including early manifestations, appearances during treatment, and late presentations. An illustrated review of imaging appearances of skeletal manifestations of SCD, with examples of common and important skeletal manifestations, is therefore presented.

Persistence and expansion of intramedullary haematopoietic marrow

In normal physiology, red marrow is present throughout the skeleton at birth, with conversion to yellow fatty marrow occurring with age. In normal adults, red marrow is only present within the axial skeleton. However, in SCD patients there is a chronic anaemic state, and this acts as a stimulus for red blood cell production, resulting in persistence and hyperplasia of appendicular red marrow in adults. Furthermore, the continual production of red blood cells results in medullary expansion and cortical thinning, and this increases the risk for pathological fractures.

Signs of intramedullary hyperplasia may be subtle on plain radiographs, with coarsening of the trabecular pattern sometimes demonstrated in the long bones. Within the skull, marrow expansion is indicated by the thinning of the inner and outer tables and widening of the diploic space.

On MR imaging, haematopoietic red marrow demonstrates isointense/low T1w and T2w signal (relative to muscle), in contrast to the normal high T1w and T2w signal returned from yellow marrow (Figure 1). If gradient-echo sequences are performed, there may be blooming artefact secondary to haemosiderin deposition from repeated blood transfusions.

Bone infarction

Bone infarction is an important skeletal pathology which occurs due to the occlusion of microvasculature supplying the bones. The abnormal red blood cells produced in SCD have a propensity to sickle within the bone marrow, leading to stasis of blood and therefore occlusion of the microvasculature, with resultant ischaemia and infarction. Clinically, acute bone infarction may present with painful bone crises, or it may be clinically silent.
Infarction commonly affects the long bones within children and adults, and there are variable plain radiographic appearances depending on the timeframe. In acute infarcts, there is often a normal appearance, although osteolysis and a periosteal reaction may rarely occur. In chronic infarcts, there may be serpiginous calcification, or more commonly patchy sclerosis (Figure 2). In non-long bones such as the spine, ribs and pelvis, there is marked sclerosis, secondary to dystrophic medullary calcification that occurs after medullary infarction. In children, the diaphyses of tubular bones within the hands and feet may become infarcted, leading to a clinical presentation of fever and swollen hands and feet, known as "hand-foot syndrome". Plain radiographs demonstrate initial periosteal reaction, followed by patchy sclerosis.

On MRI, acute bone infarcts present with signs of oedema, with low T1w and high T2w signal returned at affected areas. Similarly, high signal is seen on T1 fat-saturated sequences (Figure 3). If intravenous contrast is given, there is thin linear enhancement surrounding the affected areas. In chronic infarction, there is a classical serpiginous pattern, characterised by low T1w signal and high T2w signal outlining the red marrow. Additionally, T2w sequences may demonstrate an outline composed of both low and high signal, resulting in a "double line" appearance.

**Avascular necrosis**

Avascular necrosis is a common skeletal presentation in SCD, occurring due to microvascular occlusion and subsequent ischaemia within the epiphyses. The most frequently affected sites are the humeral and femoral heads. Initial plain radiographs are often normal, although subtle signs such as increased central density sometimes may be appreciated. As the process progresses, there may be crescentric subchondral lucency, with eventual flattening, collapse and fragmentation of the articular surface (Figure 4 and 5). The vertebral bodies are also typically affected by avascular necrosis, presenting with initial sub-endplate sclerosis, followed by collapse of the central endplates and formation of a characteristic "H" shaped vertebra (Figure 6).

Similar to bone Infarction, avascular necrosis usually presents with signs of bone marrow oedema on MRI (low T1w and high T2w signal). In established avascular necrosis, there is often a serpiginous "double-line" rim on T2w sequences, composed of an inner hyperintensity line and an outer hypointensity line, that surrounds the affected weight-bearing region (Figure 7 and 8).

**Infection**
Infections including osteomyelitis, and less commonly septic arthritis, are significant complications which are more prevalent in SCD, due to a combination of factors including reduced immunity secondary to hyposplenism (from infarction) and presence of a favourable culture medium provided by infarcted and necrosed bone. Osteomyelitis in SCD patients is usually caused by *Salmonella* bacteria species, with *Staphylococcus aureus* infections being less common. Clinically, osteomyelitis presents with localised pain and swelling of the affected region, in conjunction with fever and raised inflammatory markers. This clinical presentation is similar to that the presentation of painful bone crises, and distinction between the two entities is challenging but important in order to avoid unnecessary antibiotic treatment.

Acute osteomyelitis may often initially demonstrate normal appearances on plain radiographs, although features such as periosteal reaction, osteopaenia and sclerosis may be seen (Figure 9). Ultrasonography of osteomyelitis may be helpful, particularly in children, and may demonstrate associated soft tissue inflammation and collections, in addition to visualising cortical breaks and periosteal reaction. In septic arthritis, ultrasonography is useful in terms of confirming the presence of a joint effusion, and guiding aspiration (Figure 10 and 11).

On MRI, regions affected by osteomyelitis demonstrate low T1w signal, although this may be indistinguishable from the low T1w signal appearances of red marrow hyperplasia. Fluid sensitive sequences demonstrate high signal intensity within the affected regions, and this high signal extends into the surrounding soft tissues, in keeping with adjacent soft tissues oedema and inflammation (Figure 12). This feature of soft tissue involvement is not usually seen with bone infarct and can be used as a distinguishing characteristic. On post-contrast sequences, there is irregular rim enhancement, surrounding a non-enhancing centre, and adjacent soft tissues also demonstrate avid enhancement. MRI appearances of septic arthritis include synovial enhancement post-contrast administration, and perisynovial oedema.
Images for this section:

**Fig. 1:** MRI of the skull (sagittal T1w sequence): there is calvarial expansion and marrow hyposignal change (arrows), in keeping with red marrow reconversion and marrow hyperplasia.

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Fig. 2: Plain radiograph of the left tibia and fibula (AP and lateral): there are diffuse but subtle patchy sclerotic changes, in keeping with previous infarction.

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**Fig. 3:** MRI of the pelvis (top row - coronal T1w sequence, bottom row - coronal STIR sequence): there is diffuse low T1w signal in keeping with red marrow reconversion. Within the left femoral neck and right iliac wing, there is low T1w signal and corresponding high signal (arrows) on the STIR sequence, in keeping with marrow oedema. There is no corresponding soft tissue signal abnormality, and appearances are in keeping with acute infarcts.

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**Fig. 4:** Plain radiograph of the hips in a child (AP): there is deformity of the left hip joint with flattening and sclerosis of the left femoral head. Linear subchondral lucency is also
present within the left femoral epiphysis, in addition to irregularity of the left acetabular margin. Appearances are in keeping with avascular necrosis of the left hip.

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**Fig. 5:** CT of the left shoulder (coronal slices): there is marked volume loss and collapse of the humeral head, with scalloping and irregularity of the glenoid. Loose bodies are noted, and appearances are in keeping with established avascular necrosis and secondary osteoarthritis.

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**Fig. 6:** Plain radiograph of the chest (AP view): there is diffuse sclerosis within the ribs bilaterally in keeping with previous infarction. Note is also made of the characteristic "H" shaped vertebrae (arrowed), which occur secondary to avascular necrosis. Additionally, there is a degree of sclerosis and flattening of the humeral heads bilaterally, also in keeping with avascular necrosis.

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Fig. 7: MRI of the left shoulder (coronal T1w sequences): this is the same patient as on the CT shoulder study (Figure 5). Findings correlate with the CT study, with erosion and collapse of the humeral head again demonstrated. A large joint effusion is also seen.

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Fig. 8: MRI of the pelvis (left - coronal PD sequence, right - coronal T1w sequence): there is flattening and collapse of both femoral heads, more so on the left, in keeping with avascular necrosis.

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Fig. 9: Plain radiograph of the right femur (AP and lateral) in a child: there is extensive abnormality involving the distal diaphysis of the femur, with permeative destruction, multiple subtle areas of lucency, periosteal reaction, and fracture. The appearances are in keeping with osteomyelitis.

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**Fig. 10:** Ultrasound of the thigh (transverse orientation): there is cortical irregularity, with associated hyperechoic soft tissue formation that demonstrates increased Doppler flow. There is additional swelling and inflammation of the surrounding muscles and soft tissues. Appearances are indicative of cortical breaks and an inflammatory process, as well as phlegmon formation, suspicious for osteomyelitis related soft tissue changes in the correct clinical history.

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Fig. 11: Ultrasound of the left sternoclavicular joint: there is synovial hypertrophy and oedema of the left sternoclavicular joint, with thick and hyperechogenic fluid within it. Appearances are in keeping with septic arthritis and an ultrasound guided aspiration was performed.

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**Fig. 12:** MRI of the pelvis (top row - axial STIR sequence, middle row - axial T1w sequence, bottom row - axial T1w post-contrast fat-saturated sequence): there is generalised increased signal throughout the left pelvis and minimally in the adjacent gluteal muscles on the STIR sequence. There is corresponding rim enhancement surrounding the pelvic marrow on the T1 post-contrast sequences, with associated enhancement within the adjacent muscles. The appearances are in keeping with bone and muscular infarcts.

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Conclusion

SCD is a systemic disease arising from the production of abnormal red blood cells, with multiple skeletal manifestations that occur through different pathological mechanisms, some of which are closely similar in imaging findings. Due to variation in morbidity and treatment of these disorders, prompt and accurate diagnosis is necessary in order to facilitate appropriate and timely management. A clear understanding of the imaging appearances of these presentations is therefore important in order to enable accurate diagnosis and management.
References

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