

Received:
10 January 2022

Revised:
17 April 2022

Accepted:
19 April 2022

Published online:
10 May 2022

<https://doi.org/10.1259/bjr.20220063>

Cite this article as:

Saifuddin A, Tyler P, Rajakulasingam R. Imaging of bone marrow pitfalls with emphasis on MRI. *Br J Radiol* (2022) 10.1259/bjr.20220063.

REVIEW ARTICLE

Imaging of bone marrow pitfalls with emphasis on MRI

ASIF SAIFUDDIN, PHILIPPA TYLER and RAMANAN RAJAKULASINGAM

Department of Radiology, Royal National Orthopaedic Hospital, Stanmore, United Kingdom

Address correspondence to: Dr Ramanan Rajakulasingam

E-mail: ramanan.rajakulasingam1@nhs.net

ABSTRACT

Normal marrow contains both hematopoietic/red and fatty/yellow marrow with a predictable pattern of conversion and skeletal distribution on MRI. Many variations in normal bone marrow signal and appearances are apparent and the reporting radiologist must differentiate these from other non-neoplastic, benign or neoplastic processes. The advent of chemical shift imaging has helped in characterising and differentiating more focal heterogeneous areas of red marrow from marrow infiltration. This review aims to cover the MRI appearances of normal marrow, its evolution with age, marrow reconversion, variations of normal marrow signal, causes of oedema-like marrow signal, and some common non-neoplastic entities, which may mimic marrow neoplasms.

INTRODUCTION

Bone marrow represents a huge space within which focal and diffuse abnormalities that can mimic neoplastic disease may be identified on magnetic resonance imaging (MRI). To avoid misdiagnosing normal marrow, changes due to physiological reconversion, and lesions associated with oedema-like marrow signal intensity (OLMSI) as neoplastic pathology, radiologists should be aware of normal changes in the distribution of yellow and red marrow with age, the appearances of marrow reconversion and the commoner focal and multifocal non-neoplastic lesions that may be seen incidentally on MRI.

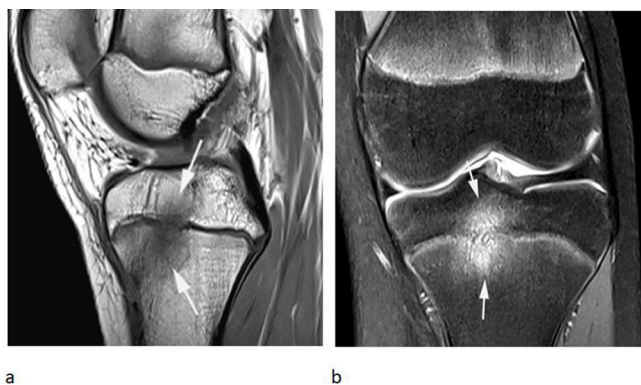
MRI APPEARANCES OF NORMAL BONE MARROW

The MRI appearances of normal bone marrow and its changes with age have been extensively reviewed in the literature,^{1,2} and will only be dealt with briefly. The signal intensity (SI) of bone marrow is dependent upon the relative proportions of yellow (inactive, fatty) and red (active, haematopoietic) marrow. The bone marrow of neonates is uniformly hypointense on T1W turbo spin echo (T1W TSE) images due to the predominance of red marrow, but by 6 months of age the epiphyses and apophyses contain yellow marrow.^{3,4} The presence of residual red marrow in the infant skeleton can make the identification and/or extent of pathological processes difficult to assess (Supplementary Figure 1). Bracken et al⁵ studied the T1W marrow SI in 19 children aged from 1 day to 3 years 10 months, finding that 69% of infant marrow sites and 24% in children > 1 year were isointense, and could therefore mimic marrow

pathology. Waitches et al⁶ demonstrated that heterogeneous fatty marrow was routinely seen in the femoral diaphysis by 12 months of age, while after 5 years of age the femoral diaphysis showed homogeneous fatty marrow. Therefore, the presence of T1W isointense metaphyseal marrow in children > 1 year should be viewed with suspicion (Supplementary Figure 2). However, it should be noted that although complete red-to-yellow marrow conversion typically finishes around 25 years of age, small areas of residual red marrow can be seen in the axial skeleton and the proximal metaphyses of major long bones.⁴

An important principle of bone marrow MRI assessment is its appearance on non-fat suppressed, non-contrast enhanced T1W TSE images,⁷ which can usually differentiate areas of red marrow, areas of OLMSI and areas of marrow replacement. This is a fundamental requirement in musculoskeletal MRI. Residual red marrow shows variable SI, which is hypointense to fat but hyperintense to skeletal muscle since it still contains ~15% fat, with fairly well-defined but irregular 'geographic' margins (Supplementary Figure 3). OLMSI has similar SI characteristics but poorly defined margins (Figure 1),⁸ and appears much more prominent on short tau inversion recovery (STIR) or fat suppressed T2W FSE sequences (Figure 2). This difference between T1W and STIR SI is an important feature of OLMSI (Supplementary Figure 4), which is not seen with marrow replacement. OLMSI also shows enhancement following contrast. Marrow replacement typically appears isointense or hypointense to skeletal muscle, with relatively sharp margins (Supplementary Figure 5).^{1,9} Within the

Figure 1. A 13-year-old girl presenting with left knee pain. (a) Sagittal T1W TSE and (b) coronal STIR MR images show a bone marrow oedema pattern either side of the proximal tibial physis (arrows), the features being those of a focal peri-physeal oedema zone (FOPE) lesion.



spine, a similar comparison can be made between marrow SI and the intervertebral disc (IVD), with lesions that are hyperintense to the IVD almost always representing red marrow (Figure 3), while lesions which are iso- or hypointense to the IVD almost invariably representing marrow infiltrative disorders.¹⁰ However, in the paediatric skeleton, T1W marrow SI is expected to be hypointense to the IVD under 6 months of age and may still be hypointense up to 2 years of age. Marrow SI may also be lower than that of the IVD in adults in the thoracic spine, due to the relatively higher T1W SI of thoracic IVDs.¹¹

MRI APPEARANCES OF BONE MARROW VARIANTS

There may be variations in the distribution of yellow and red marrow within the vertebral bodies.^{2,11} In children and young adults, it is relatively common to find prominent fatty marrow around the basi-vertebral veins (Supplementary Figure 6). Conversely, red marrow may be more prominent adjacent to the vertebral endplates which represent a metaphyseal equivalent, or

Figure 2. A 19-year-old female who presented with medial shin pain and swelling. (a) Coronal T1W TSE and (b) STIR MR images show prominent oedema-like marrow signal intensity (arrows) in the proximal tibial metaphysis and reactive pes anserinus bursitis (arrowheads). (c) Coronal CT MPR demonstrates the intracortical osteoid osteoma nidus (arrow) with associated endosteal sclerosis and periosteal response (arrowheads).



Figure 3. A 65-year-old female referred for investigation of an incidental lesion in the L3 vertebral body. Sagittal T1W TSE MR image of the lumbar spine shows an oval lesion (arrow) which is hyperintense to both the intervertebral disc and skeletal muscle consistent with a focal area of red marrow.



in the central anterior aspect of the vertebral body (Supplementary Figure 7). In older patients, the spinal marrow may appear generally heterogeneous with multiple islands of fatty marrow due to osteoporosis, in which case it is important to correlate the appearances on T1W, T2W and STIR sequences (Supplementary Figure 8). Conversely, marrow heterogeneity may be due to the presence of multiple nodular or more diffuse areas of red marrow, which are more difficult to differentiate from marrow replacement. In such cases, the use of quantitative chemical shift imaging (CSI) can be of value by demonstrating marked SI drop on the out-of-phase (OOP) sequence (Supplementary Figure 9).¹²

Several marrow variations in the paediatric skeleton need to be recognised and not mistaken for pathological processes. Pal *et al*¹³ described either multiple discrete or more confluent areas of reduced T1W and increased T2W/STIR SI in the marrow of children's feet, so-called 'spotty feet' (Supplementary Figure 10), seen in 63% of symptomatic and 57% of asymptomatic individuals and being symmetrical when both feet were imaged. Similar changes were reported in 11% of the foot and ankle bones in 59% of children under the age of 16 years, most commonly in the

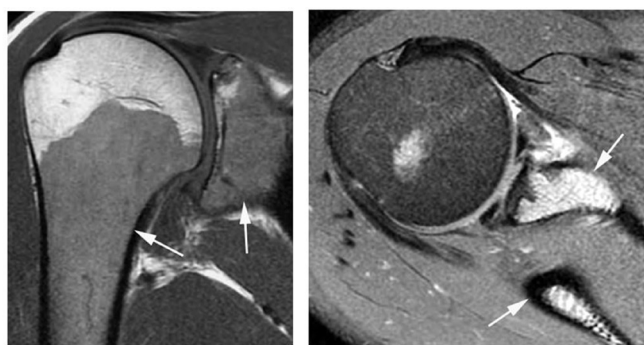
calcaneus (54%), talus (35%) and navicular (35%), typically at the endosteal surface and likely representing residual red marrow.¹⁴

Zbojniec et al¹⁵ described areas of OLMSI adjacent to the open physes around the knee in adolescents, calling these FOPE (focal periphyseal edema zone) lesions (Figure 1). These occurred in children from 11 years 9 months to 15 years eight months, measuring 2–27 mm in dimension. FOPE is seen as a flame-shaped pattern of OLMSI around the central portion of a closing physis.¹⁵ The OLMSI pattern is typically eccentric to the central portion of the physis. Whilst normally asymptomatic, the central portion of the physis may be susceptible to trauma/stress during physeal closure due to decreased elasticity. Therefore, FOPE should only be considered as a source of pain if no other finding is seen on MRI and the corresponding area is clinically symptomatic. Reassuringly, it is a self-limiting process and the oedema usually resolves once/soon after physeal closure with no active management required.¹⁶

MRI APPEARANCES OF MARROW RECONVERSION

Bone marrow reconversion occurs when red marrow replaces yellow marrow in the reverse pattern to that seen in normal yellow-to-red marrow conversion. It occurs under conditions of increased haematopoietic demand, which may be physiological due to conditions such as obesity, cigarette smoking, in high endurance athletes and following treatment with granulocyte-colony stimulating factor (GCSF). Alternatively, it may be pathological such as in severe chronic anaemias, diabetes and chronic respiratory disease.^{1,17} Areas of marrow reconversion still have the same SI characteristics of red marrow, being hypointense to normal marrow fat on T1W but still mildly hyperintense to skeletal muscle, allowing differentiation from marrow infiltration (Figure 4).

Figure 4. A 37-year-old male with known myelodysplastic syndrome who presented with right shoulder pain. (a) Coronal T1W TSE and (b) axial SPAIR MR images show diffuse reduction of T1W marrow SI in the proximal humeral metaphysis and glenoid (arrows-a) with corresponding increased marrow SI on the SPAIR sequence (arrows). The marrow is still hyperintense to skeletal muscle on T1 indicating marrow reconversion as opposed to marrow replacement from a neoplastic process.



a

b

On MRI, areas of red marrow reconversion in the appendicular skeleton tend to be fairly homogeneous and symmetrical, and if severe enough may extend into the epiphyses (Supplementary Figure 11). However, marrow reconversion in the spinal column may appear much more heterogeneous with areas of red marrow embedded in the underlying yellow marrow, potentially mimicking metastases or myeloma. However, using the basic principle of T1W SI being hyperintense to skeletal muscle or the IVD helps make this differentiation. In cases of doubt, CSI can be utilised, which demonstrates marked SI drop on the OOP sequence due to the fat content of red marrow.

The prevalence and relevance of residual red marrow on knee MRI have been investigated. Vo et al¹⁸ reported on 327 patients aged 31–41 years and only identified residual red marrow in 18.8% of females, more commonly in the femur than tibia. This was associated with obesity. Gonzales et al¹⁹ studied 457 knee MRIs and identified a relationship between low haemoglobin level and a greater degree of red marrow reconversion, suggesting that females who show diffuse red marrow reconversion in the distal femur (Supplementary Figure 12), proximal tibia and proximal fibula should undergo investigation for anaemia. Marrow reconversion has also been seen in association with heavy smoking,²⁰ endurance athletes,²¹ male professional cyclist²² and in obstructive sleep apnoea.²³

Prominent red marrow reconversion occurs following treatment with granulocyte-colony stimulating factors, which are commonly used to manage neutropenia during chemotherapy.²⁴ Marrow reconversion may occur as soon as 16 days following commencement of treatment, and may be either patchy (Supplementary Figure 13) or more homogeneous (Figure 5), potentially mimicking disease progression and/or metastatic disease.

Diffuse marrow reconversion

Diffuse marrow reconversion manifesting as reduction of T1W SI and variable T2W/STIR SI is commonly seen in various haematological conditions such as severe chronic anaemias,²⁵ myeloproliferative disorders^{26,27} and myelodysplastic syndrome.²⁸ In the absence of a known prior clinical history, such marrow changes may be mistaken for neoplastic infiltration.

Severe anaemia occurs in the haemoglobinopathies, including beta-thalassaemia²⁹ and sickle cell disease (SCD).³⁰ The resulting marrow hyperplasia produces marked reduction of T1W SI in both conditions (Supplementary Figure 14), but considering that the diagnosis is usually clinically evident from early childhood there should be no concern that the changes represent infiltration. Additional features of beta-thalassaemia include reduction of T2W marrow SI due to iron overload from repeat blood transfusions, and para-osseous soft tissue masses due to extramedullary haematopoiesis (Supplementary Figure 15). Similar marrow changes occur in SCD, which can be complicated by osteonecrosis (Supplementary Figure 16) and osteomyelitis. These latter conditions may result in focal marrow lesions on a background of diffuse marrow hyperplasia that could be mistaken for neoplastic lesions (Figure 6).

Figure 5. A 10-year-old boy with a Ewing sarcoma arising from the right pubic bone. (a) Coronal T1W TSE MR image at presentation shows the primary tumour (arrow) with normal fatty marrow in the imaged portion of the pelvis and proximal femora. (b) Coronal T1W TSE MR image of the pelvis and (c) Sagittal T1W TSE MR image of the spine following neoadjuvant chemotherapy show widespread diffuse reduction of marrow SI due to marrow hyperplasia following granulocyte-colony stimulating factor treatment, but mimicking metastatic disease.

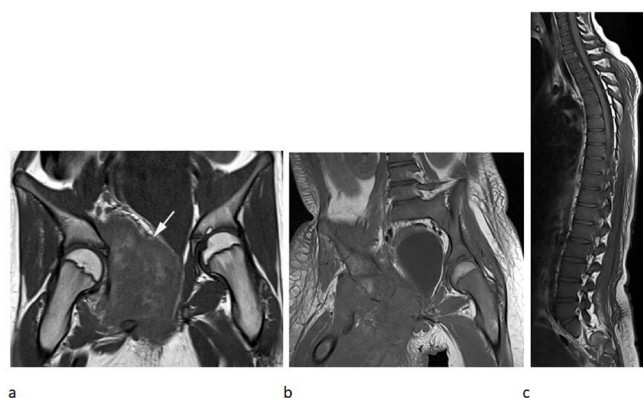


Figure 6. A 20-year-old female with known sickle cell disease imaged for right arm pain due to a possible bone tumour. (a) Coronal T1W TSE and (b) STIR MR images show an expansile lesion in the humeral diaphysis (arrows) with an associated inflammatory soft tissue mass (arrowheads-b). The lesion demonstrates a 'penumbra sign' on T1W, the overall features being consistent with subacute osteomyelitis. Note the underlying red marrow hyperplasia (thin arrows).

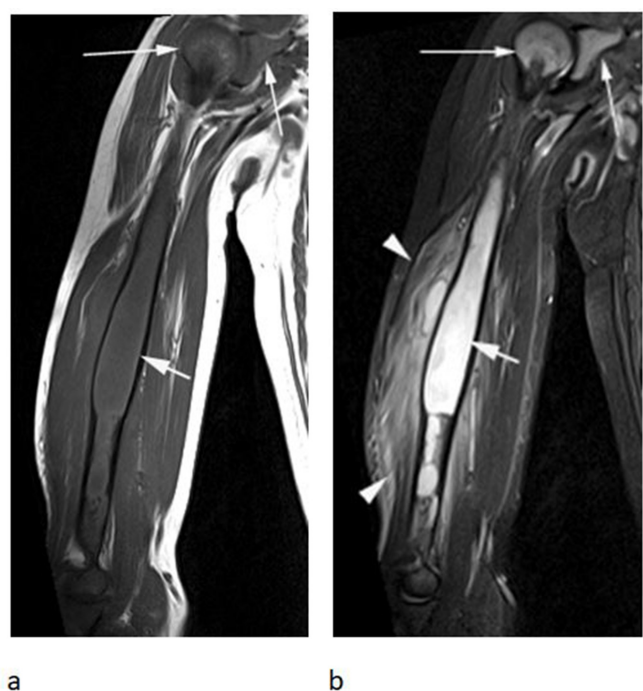


Figure 7. A 93-year-old male with known bladder cancer who presented with an undisplaced fracture of the right femoral neck. Marrow changes were thought to be secondary to metastases. (a) Coronal T1W TSE MR image of the pelvis shows heterogeneous reduction of T1W marrow SI (arrows). (b) Coronal CT MPR of the abdomen and pelvis shows diffuse medullary sclerosis throughout the spine (arrows) and moderate splenomegaly (arrowhead), the combined features being consistent with myelofibrosis.

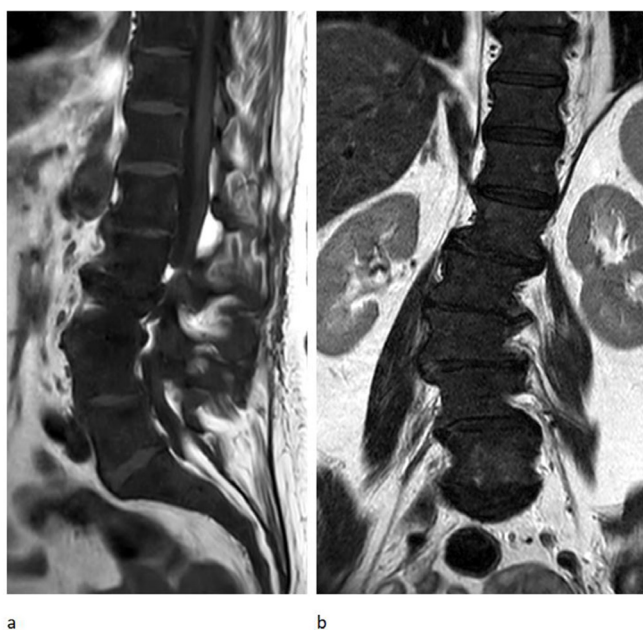


The myeloproliferative disorders include polycythaemia vera (PV), essential thrombocythaeima (ET), primary myelofibrosis (PMF) and chronic myeloid leukaemia (CML).^{26,27} Common clinical features include splenomegaly, thrombosis, bleeding and extramedullary haematopoiesis resulting in hepatosplenomegaly. The bone marrow may show reduction of T1W marrow SI due to unregulated cell proliferation ([Supplementary Figure 17](#)). Soft tissue changes include extramedullary haematopoiesis and splenomegaly. In primary myelofibrosis,³¹ marrow SI changes are a manifestation of bone marrow fibrosis, which may also occur in end-stage PV and ET (secondary myelofibrosis). On radiographs and CT, diffuse marrow sclerosis may be seen ([Figure 7](#)). This combination of marrow changes needs to be distinguished from diffuse osteoblastic metastatic disease ([Figure 8](#)).

The myelodysplastic syndromes represent a group of clonal haematological stem cell disorders which commonly present with anaemia, bruising/bleeding, and recurrent/persistent infections due to deficiencies of various blood cells.^{11,28} T1W marrow SI is diffusely reduced due to increase in marrow cellularity, and of variable SI on T2W and STIR sequences ([Figure 4](#)). Iron overload due to repeated transfusions may result in further reduction of marrow SI, particularly on T2* gradient echo sequences.

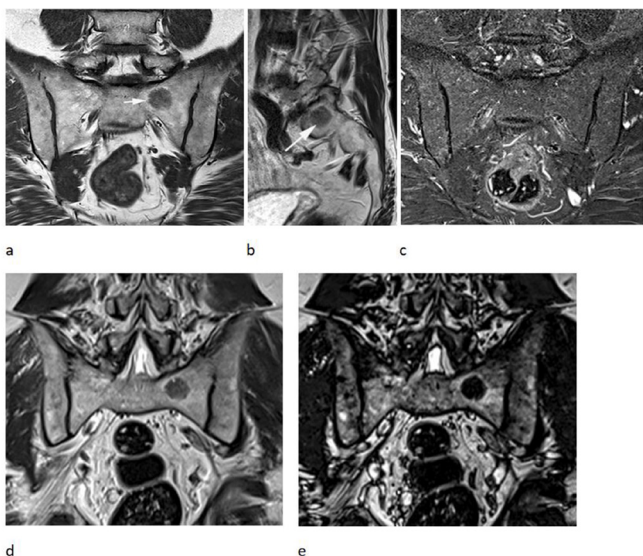
Systemic mastocytosis (SM) is another haematological condition that may result in diffuse marrow changes,³² the condition being subcategorised into indolent (ISM), smouldering (SSM) and advanced (AdvSM). Abnormal marrow patterns are most commonly seen in SSM and AdvSM.³³ Changes include an 'activated pattern' where there is diffuse reduction of T1W SI and diffuse hyperintensity on STIR, a diffuse sclerotic pattern with reduction of both T1W and STIR SI, a 'small-spotted sclerotic pattern' with tiny focal areas of reduced T1W and STIR SI which correspond to osteoblastic foci on radiography and CT, and the presence of well-defined lytic lesions which are hypointense

Figure 8. A 78-year-old female with known breast cancer. (a) Sagittal T1W TSE and (b) coronal T2W FSE MR images of the lumbar spine show diffuse profound reduction of marrow SI, shown on biopsy to be due to osteoblastic metastatic disease.



on T1W and hyperintense on STIR. Clearly, these changes can mimic metastatic disease, in particular the 'small-spotted pattern' may be mistaken for osteoblastic metastases.

Figure 9. A 79-year-old male with an incidentally identified left sacral alar marrow lesion. (a) Coronal T1W TSE, (b) sagittal T2W FSE and (c) coronal STIR MR images show an irregular oval lesion (arrows-a,b) which is slightly hyperintense to skeletal muscle on T1W and hypointense on T2W, but is occult on STIR. There is no reactive marrow oedema. (d) In-phase and (e) out-of-phase T1W GrE chemical shift imaging shows very marked SI drop on the out-of-phase sequence calculated at 85% indicating a significant fat content allowing a confident diagnosis of FNMH.



Multiple myeloma (MM) presents with five distinct patterns of marrow involvement on MRI; diffuse, focal, combined diffuse and focal, variegated, and normal. Non-malignant marrow patterns mimicking diffuse MM include haematopoietic marrow hyperplasia, while heterogeneous marrow in the elderly can mimic the variegated pattern. Differentiation is aided by careful assessment of fat and fluid sensitive MR images, as well as quantitative techniques such as CSI and FDG-PET.³⁴ Whole body-diffusion-weighted MRI (WB-DWI) is now considered the gold standard modality in imaging patients with asymptomatic myeloma and solitary plasmacytoma.³⁵ WB-DWI uses the apparent diffusion coefficient (ADC) value to quantify disease burden, overtaking FDG-PET CT for diagnosis of small marrow lesions, assessing disease burden and response to therapy.³⁵

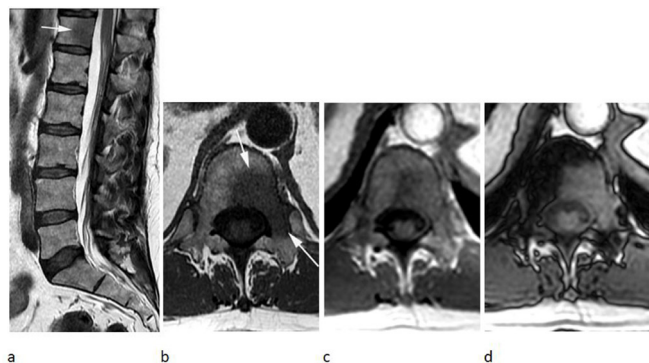
Incidental marrow lesions

Incidental marrow lesions are occasionally identified on MRI. Shah et al³⁶ reviewed 110 patients with no previous history of malignancy in whom MRI demonstrated an incidental marrow lesion. Of these, 24 underwent further investigation and six were subsequently diagnosed with a malignancy. Similarly, Carlson et al³⁷ investigated the prevalence and clinical significance of incidental vertebral marrow signal abnormalities (VMSAs) on thoracolumbar spine MRI. Of 1503 patients, 65 (4%) had a VMSA of which only one was diagnosed with a malignant lesion (multiple myeloma).

Focal nodular marrow hyperplasia (FNMH) is a form of marrow reconversion which appears as relatively well-defined round/oval or irregular areas of marrow hyperplasia that may be solitary (Figure 3) or multifocal. Rajakulasingam et al³⁸ described the detailed imaging features of FNMH. In a study of 53 patients with a mean age of 58 years, MRI demonstrated a poorly defined round/oval lesion which was isointense or mildly hyperintense to skeletal muscle on T1W, had low SI on T2W FSE images and was commonly occult on STIR (Figure 9a–c). There was no associated marrow oedema. All patients had follow-up MRI, with all lesions remaining stable or partially resolving. In-phase (IP) and OOP CSI was obtained in 31 cases, with 28 (90.3%) showing >20% SI drop on the OOP sequence (Figure 9d and e), while 3 (9.7%) demonstrated <20% SI drop. CT was undertaken in 26 cases, with 17 (65.4%) showing mild medullary sclerosis. SPECT-CT was available in four and FDG PET-CT in 2, all showing mild increased uptake. Focal uptake was noted in 3 of 8 patients on bone scintigraphy. Approximately 60% of lesions were located in the spine, with the femur, sacrum and ilium being other relatively common sites. Many patients had a pre-existing history of non-skeletal malignancy, with the identified lesions referred for biopsy as potential metastases. This study highlighted the value of quantitative CSI for establishing the diagnosis in cases where the lesion was not particularly hyperintense on T1W. It is important when performing CSI to make formal region of interest measurements rather than a simple subjective assessment, which can be misleading (Figure 10). FNMH mimicking vertebral metastasis on FDG-PET has been previously reported.³⁹

FNMH must be differentiated from bone metastases. Shigematsu et al⁴⁰ compared the MRI features of 8 patients with suspected

Figure 10. A 51-year-old male being investigated for low back pain. (a) Sagittal T2W FSE and (b) axial T1W TSE MR images show an incidental area of reduced marrow SI in the left side-of T12 (arrows-a,b). (c) In-phase and (d) out-of-phase T1W GrE chemical shift imaging shows apparent increased SI on the out-of-phase sequence. However, following actual ROI measurements, a SI drop of 58% was calculated indicating a significant fat content allowing a diagnosis of focal nodular marrow hyperplasia.



vertebral metastases later proven to represent hyperplastic red marrow/FNMH, with 24 patients who had proven spinal metastases. All 8 cases of red marrow/FNMH were hypointense on T1W and T2W, and the T2W SI was significantly different between the two entities with all cases of red marrow/FNMH being hypointense. FDG-PET showed mild increased uptake in all cases of red marrow/FNMH, but the maximum standard uptake value (SUVmax) was significantly lower than that of metastases (2.72 vs 6.46). CT attenuation values of red marrow/FNMH were equal to or slightly greater than that of adjacent normal vertebral marrow (189.8 vs 93.7HU), being significantly different from metastases. Bone scintigraphy showed normal uptake for all cases of red marrow/FNMH, which was not the case for metastases.

Quantitative CSI using IP and OOP Dixon sequences with a short TE and low flip angle is highly accurate in the differentiation of

Figure 11. A 49-year-old female investigated for low back pain. (a) Coronal T1W TSE and (b) axial T2W FSE MR images of the lumbosacral junction show an area of reduced T1W and T2W SI in the left side-of L5 (arrows) which has a rim of T2W hyperintensity (arrowhead-b) consistent with a 'halo' sign. Biopsy revealed a diagnosis of breast metastasis.



benign and malignant marrow lesions,⁴¹ and both FDG-PET and CSI are highly accurate in differentiating intertrabecular metastases from hyperplastic marrow lesions.⁴² Other MRI techniques that have been utilised for differentiating hyperplastic red marrow/FNMH from metastases/malignant marrow lesions include intravoxel incoherent motion diffusion-weighted (DWI) MRI,⁴³ proton density fat fraction, and simultaneous R2* and DWI assessing apparent diffusion coefficient (ADC) values.^{44,45} Our preference is to use low TE low flip angle T1W CSI with SI drop >20% at 1.5T and >25% at 3T between the IP and OOP sequences taken as representing FNMH (Figures 9 and 10),³⁸ while a SI drop lower than these values indicates a marrow replacing lesion which may be either non-neoplastic, benign or malignant.⁴⁶ A pitfall of low TE low flip angle T1W CSI is anomalous increase in SI seen on OOP sequences, which correlates with marrow sclerosis or matrix mineralisation presumably due to susceptibility artefact.⁴⁷ This may result in <20% SI drop in cases of FNMH since mild marrow sclerosis is a feature of this condition.³⁸ In such situations, CSI using a T2W FSE Dixon sequence may be of value, since this appears to be more reliable for the assessment of sclerotic lesions.⁴⁸

Due to its low T2W SI, FNMH may be mistaken for osteoblastic metastases. Schweitzer *et al*⁴⁹ described the 'bull's-eye' and 'halo' signs as discriminators between these conditions. A 'bull's-eye' represented an area of increased T1W SI in the centre of a lesion, and was a very reliable indicator of FNMH with sensitivity of 95% and specificity of 99.5%. Conversely, a 'halo' represented a rim of high T2W SI around a lesion with sensitivity of 75% and specificity of 99.5% for a metastasis (Figure 11). In patients with high-grade appendicular bone sarcomas, skip metastases are identified on T1W TSE whole bone MRI in 16.3% of cases.⁵⁰ FNMH may mimic skip lesions in this clinical setting, and can usually be differentiated based on T1W TSE SI characteristics.⁵¹ In cases of doubt, quantitative CSI can be used.

MRI OF NON-TRAUMATIC OEDEMA-LIKE MARROW SIGNAL INTENSITY

Differentiation between OLMSI and marrow replacement due to a neoplastic process is another basic requirement of musculoskeletal MRI reporting. OLMSI may be mistaken for neoplastic marrow infiltration, and vice versa (Figure 12). The MRI features of OLMSI have already been described, but additional features are its relatively poor identification on PDW FSE and T2*W gradient echo sequences (Supplementary Figure 18), which are unreliable for the assessment of marrow pathology.

OLMSI can be divided into those with a known and unknown aetiology, with well-recognised causes including trauma, degenerative, inflammatory, vascular, infectious, neoplastic, iatrogenic, metabolic and neurological diseases.⁵² OLMSI of unknown aetiology includes conditions variously termed transient bone marrow oedema syndrome, transient regional osteoporosis, transient regional bone marrow oedema and migratory osteoporosis.⁵³

Figure 12. A 46-year-old male who presented with non-traumatic left hip pain. (a) Coronal PDW FSE, (b) axial SPAIR and (c) axial oblique T2*W GrE MR images of the left acetabulum demonstrate no obvious marrow lesion on the PDW FSE image although there is mild increased SI in the adjacent soft tissues (arrows-a). Increased marrow SI is seen on the SPAIR image (arrow-b) which could be consistent with oedema-like marrow SI, but the increased SI on the T2*W GrE image (arrow-c) is not consistent with OLMSI. No T1W TSE sequence had been obtained, and a diagnosis of occult fracture was made. A year later, the patient re-presented with progression of the marrow abnormality and a large extraosseous soft tissue mass, diagnosed as high-grade chondrosarcoma.

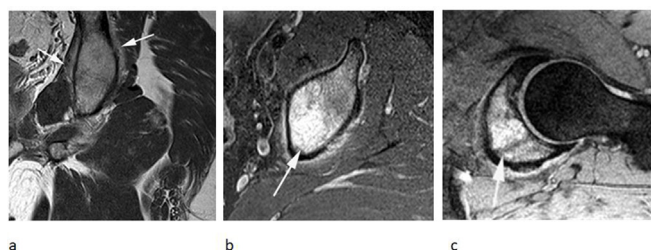


Figure 13. A 66-year-old female who presented with acute onset low back pain. (a) Sagittal T1W TSE and (b) sagittal STIR MR images demonstrate oedema-like marrow signal intensity in the L3 vertebra (arrows) with some residual marrow fat evident. A transverse hypointense fracture line (arrow-head-b) is also present, and there is a healed benign vertebral compression fracture at the level below. The combined features are consistent with an acute benign vertebral compression fracture.



Benign Vertebral Compression Fractures

Benign vertebral compression fractures (BVCs) must be differentiated from pathological collapse, since both can present with areas of reduced T1W and increased T2W/STIR SI. MRI findings suggestive of BVCs include coexisting healed BVCs, areas of residual marrow fat, sparing of the pedicles, a band-like shape of abnormal SI possibly containing a hypointense fracture line (Figure 13), the presence of a 'fluid sign' (Figure 14), and focal posterior vertebral border convexity or retropulsion. Features indicative of pathological collapse include the presence of other infiltrative vertebral lesions suggestive of metastases, the presence of a para-spinal mass, involvement of the neural arches, complete replacement of normal bone marrow, the presence of an epidural mass, and diffuse convexity of the posterior vertebral border.⁵⁴ Several quantitative MRI techniques have demonstrated reliability in differentiating BVCs from pathological fractures, including proton density fat fraction measurement, quantitative evaluation of T2* relaxation time,^{55,56} qualitative and quantitative analysis of a single T2W FSE Dixon sequence,⁵⁷ and ADC values.⁵⁸

Stress and pathological fractures

Stress fractures can present with bone pain and a marrow abnormality in the absence of a history of trauma,⁵⁹ thus mimicking a neoplastic process. MRI shows OLMSI and the diagnosis is indicated by the demonstration of a fracture line, which is an extremely rare feature in the setting of malignant marrow infiltration. Fracture lines may be either cortically based and often associated with cortical thickening and periosteal oedema, or within the cancellous bone appearing as a hypointense line which commonly runs perpendicular to the bone cortex (Supplementary Figure 19). Diagnostic difficulty may arise in the differentiation of pelvic/sacral insufficiency fractures in patients who have undergone previous radiotherapy for prostate or cervical cancer. Again, the demonstration of a fracture line is key to the diagnosis (Figure 15), but in this situation the addition of DWI may be of added benefit.⁶⁰ When OLMSI is difficult to differentiate from marrow infiltration, CSI may be of value by demonstrating >20% SI drop on the OOP sequence. However, insufficiency fractures are a recognised cause of anomalous increase in OOP SI due to trabecular impaction and reparative sclerosis, which can result in diagnostic difficulty.⁴⁷

Subchondral insufficiency fractures involve the articular surfaces, most commonly in the femoral head and around the knee.⁶¹ They are commonest in the setting of osteoporosis, typically presenting with severe acute onset hip or knee pain with normal radiographs, possibly apart from underlying osteoarthritis. MRI demonstrates excessive OLMSI which commonly fills the femoral head or the involved femoral condyle, and a subchondral hypointense fracture line which runs parallel to the articular surface (Supplementary Figure 20). The identification of the fracture line is of paramount importance in distinguishing the condition from early avascular necrosis or transient migratory osteoporosis. If not recognised, they may result in collapse of the articular surface.

Atypical femoral fractures (AFFs) are insufficiency fractures commonly associated with bisphosphonate treatment. Typical features of AFFs are location in the lateral subtrochanteric region/diaphysis, and a transverse or short oblique fracture configuration.^{59,62} In a setting of previous malignancy, the development of new

Figure 14. An elderly patient who presented with low back pain. Sagittal T2W FSE MR image shows a linear area of fluid SI (arrow) at the anterosuperior aspect of the L2 vertebral body where there is a compression fracture of the superior endplate, the 'fluid sign' being significantly associated with benign vertebral compression fractures.



bone pain and an imaging abnormality may be mistaken for metastatic disease. Typical MRI features include focal cortical thickening with adjacent endosteal OLMSI and periosteal oedema.⁶³

Pathological fractures occur in the setting of an underlying bone lesion, most commonly a metastasis and less commonly a primary bone tumour.^{59,64} In the paediatric population, pathological fractures are a strong indicator of benign bone lesions when taking into

Figure 15. A 77-year-old female who presented with left buttock pain. (a) Coronal oblique T1W TSE and (b) axial SPAIR MR images demonstrate oedema-like marrow signal intensity within the left sacral ala (arrows) together with a hypointense fracture line (arrowhead-b) running perpendicular to the cortex indicative of a sacral insufficiency fracture.

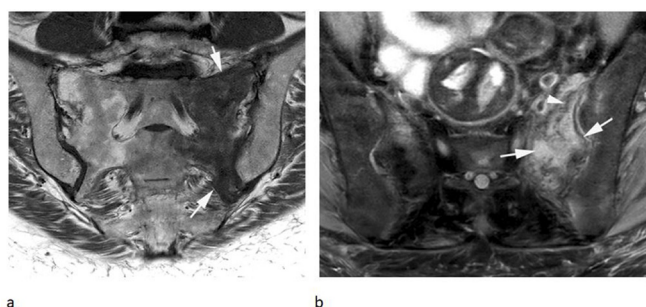
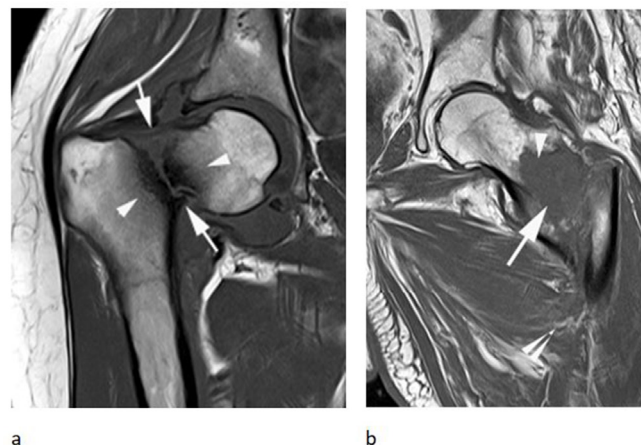


Figure 16. (a) A 26-year-old female who presented with acute right hip pain. Coronal T1W TSE MR image shows a fracture (arrows) through the inferior aspect of the femoral neck with oedema-like marrow signal intensity in the adjacent bone (arrowheads), indicative of a non-pathological fracture. (b) A 79-year-old male who presented with acute left hip pain. Coronal T1W TSE MR image shows a displaced intertrochanteric fracture (arrow) with a relatively well-defined area of marrow replacement in the adjacent bone (arrowheads), indicative of a pathological fracture.



account the radiographic appearances of the primary tumour.⁶⁵ Imaging plays an important role in the prediction of fracture risk,⁶⁶ and also in the differentiation of pathological from non-pathological fractures. The major discriminating factor is the T1W marrow pattern at the fracture site, with non-pathological fractures showing OLMSI (Figure 16a) while pathological fractures demonstrate a relatively well-defined area of marrow replacement (Figure 16b). Differentiation of stress fractures from pathological fractures is optimal on MRI, the typical features of a pathological fracture being well-defined T1W marrow signal, endosteal scalloping, muscle signal abnormality, and a soft-tissue mass.⁶⁷

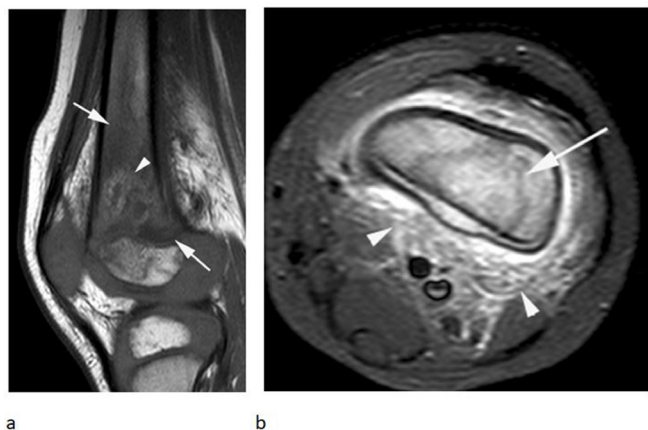
Tumour-Induced OLMSI

OLMSI secondary to a variety of primary bone tumours is a relatively common finding, which may result in diagnostic uncertainty.^{68,69} Gao *et al*⁷⁰ reported the incidence of OLMSI associated with benign tumours and tumour-like lesions as 35.7%, the commonest lesions being Langerhans cell histiocytosis, osteoblastoma, osteoid osteoma, and chondroblastoma. Of 107 cases associated with OLMSI, 45.8% were misdiagnosed as malignant tumours on MRI. In the case of osteoid osteoma, the predominant abnormality on MRI is OLMSI and the nidus may be difficult to identify or may be occult, in which case CT should be undertaken (Figure 2).⁷¹ Peri-tumoural oedema also makes assessment of intramedullary tumour extent difficult, particularly in the paediatric skeleton. In such situations, OOP T1W GrE Dixon sequences may be of value since they will demonstrate marked SI drop in the peri-tumoural oedema.⁷²

Bone infection

Acute and subacute osteomyelitis (Brodie's abscess) typically present in the paediatric and young adult age group.^{73,74} MRI

Figure 17. A 3-year-old boy who presented with knee pain and swelling. (a) Sagittal T1W TSE and (b) axial STIR MR images show prominent oedema-like marrow signal intensity (arrows) in the distal femoral metaphysis with focal residual marrow fat (arrowhead-a), periosteal elevation and soft tissue oedema (arrowheads-b) due to acute osteomyelitis.



demonstrates prominent OLMSI. The identification of persistent focal or diffuse fat SI within the abnormal marrow is a frequent finding in acute osteomyelitis (Figure 17),⁷⁵ while the 'penumbra sign' on unenhanced T1W MRI is highly specific for Brodie's abscess (Figure 6).^{76,77} Multifocal skeletal tuberculosis can also mimic metastatic disease.⁷⁸

CRMO and SAPHO syndrome

Chronic recurrent multifocal osteomyelitis (CRMO) and synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) syndrome are chronic relapsing inflammatory musculoskeletal conditions commonly associated with skin disorders such as palmoplantar pustulosis and acne, with characteristic imaging features in the form of synovitis, osteitis and hyperostosis. CRMO predominantly occurs in children/adolescents and SAPHO in adults.⁷⁹ Both conditions present with focal or multifocal OLMSI

Figure 18. A 12-year-old girl referred for the investigation of multifocal skeletal lesions. (a) Sagittal T1W TSE and (b) axial SPAIR MR images of the spine demonstrate oedema-like marrow signal intensity (arrows) within the T12 vertebra. (c) Coronal STIR MR image of the knees shows further oedema-like marrow signal intensity lesions around both knees, the combined features being typical of CRMO.

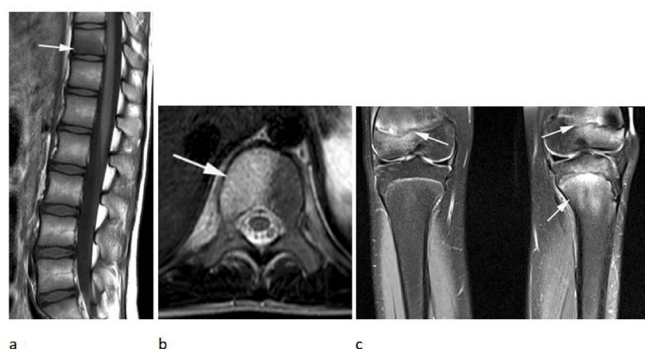
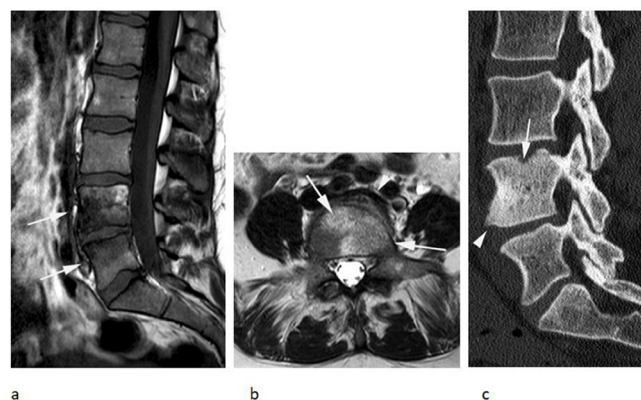


Figure 19. A 36-year-old female being investigated for low back pain. (a) Sagittal T1W TSE and (b) axial T2W FSE MR images of the lumbar spine demonstrates oedema-like marrow signal intensity (arrows) within the L4 and L5 vertebrae. (c) Sagittal CT MPR demonstrates diffuse sclerosis of L4 indicative of osteitis (arrow) and hyperostosis at the anteroinferior margin of L4 (arrowhead), the combined features being typical of SAPHO.



with the anterior chest wall and spine being common locations of SAPHO,^{80–82} and the medial clavicle, spine, pelvis and long bone metaphyses being typical sites in CRMO.⁸³ Multifocal skeletal involvement in both conditions can be assessed with whole-body MRI.^{84,85} Medial clavicular involvement in CRMO can result in marked bone expansion mimicking tumours such as Ewing sarcoma, although malignant bone tumours in the medial clavicle are very rare in the paediatric population.^{86,87} CRMO is a relatively common cause of paediatric vertebral collapse,⁸⁸ and this together with the presence of widespread skeletal lesions can mimic metastatic disease, LCH or leukaemia (Figure 18). Spinal involvement in SAPHO is characterised by focal/multifocal areas of OLMSI with corresponding marrow sclerosis on radiography or CT indicative of active osteitis, cortical erosions and hyperostosis which classically involves the anterolateral vertebral margin (Figure 19). Progression to vertebral ankylosis is a recognised complication.

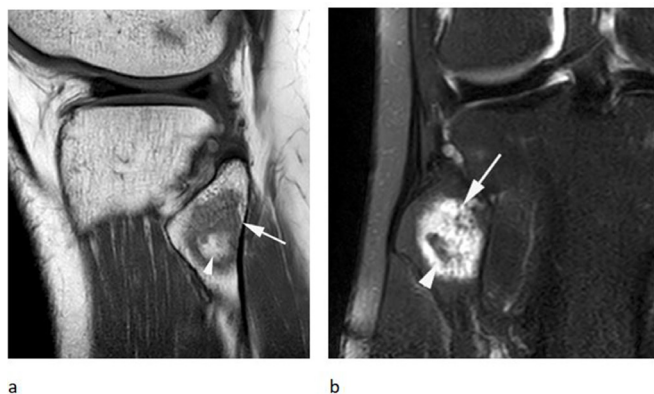
Bone infarction

The appearances of healed marrow infarction are well-recognised, the findings including the presence of normal medullary fat surrounded by a serpiginous margin of low T1W SI and a 'double-line' sign on T2W images. Acute marrow infarcts may appear as an irregular area of OLMSI which contains central fat SI, the latter being indicative of the diagnosis (Figure 20).^{89,90} A follow-up MRI study in 3–6 months will demonstrate the typical appearances of healed medullary infarction. Cystic degeneration is also a rare complication of medullary bone infarction, appearing as a predominantly fluid SI lesion with or without a peripheral fat SI margin (Supplementary Figure 21).⁹¹

Serous Atrophy of Bone Marrow

Serous atrophy of bone marrow (SABM), also termed gelatinous bone marrow transformation, is a potentially reversible condition characterised by fatty marrow atrophy with deposition of gelatinous substances in the marrow space.⁹² Prolonged

Figure 20. A 46-year-old female who was investigated for knee pain. (a) Sagittal T1W TSE and (b) coronal STIR MR images show an irregular area of oedema-like marrow signal intensity (arrows) in the fibular head with central fat SI (arrowheads), consistent with an immature marrow infarct.



starvation or other conditions bringing about lipolysis including anorexia nervosa, hypoalbuminaemia, alcohol toxicity, aplastic anaemia among many others are common underlying causes^{92,93}

MRI typically shows reduced SI of bone marrow and subcutaneous fat on T1W TSE sequences, mimicking the appearances of a fat saturated sequence even although fat saturation has not been applied.⁹⁴ Conversely, increased marrow and subcutaneous SI on fluid sensitive sequences appears as failed fat suppression,

often deemed a technical error.⁹⁴ The increased water-to-fat ratio on fluid sensitive sequences increasing T1 and T2 relaxation times is termed the 'flip-flop' effect on MRI.⁹³ However, the somewhat confusing MRI findings can be confirmed using CSI such as the Dixon technique, which should highlight fat depletion and water predominance thus avoiding misinterpretation and further unnecessary imaging. Marrow changes are seen to be focal initially and then more diffuse in severe/chronic stages of the underlying disease. It is important to note that in serous atrophy, the marrow changes tend to first occur at the distal extremities while malignant infiltrative processes typically affect red marrow rich areas such as the axial skeleton.^{93,94} Additionally, serous marrow does not enhance following contrast, unlike a malignant process.^{93,94}

CONCLUSIONS

MRI appearances of normal marrow display variations not only with age but also with a wide variety of benign processes, as discussed above. Some of these may even cause diffuse alteration in SI, providing a diagnostic dilemma for the radiologist. Recalling the normal composition of bone marrow and the process of conversion/re-conversion is a basic requirement in the understanding of marrow imaging. Additionally, knowing how this changes with variations in subjects health state, as well as in a variety of benign pathologies is essential in not over-calling normal/benign marrow patterns as malignant pathological states, leading to unnecessary further work-up and potential patient harm.

REFERENCES

- Chiarilli MG, Delli Pizzi A, Mastrodicasa D, Febo MP, Cardinali B, Consorte B, et al. Bone marrow magnetic resonance imaging: physiologic and pathologic findings that radiologist should know. *Radiol Med* 2021; **126**: 264–76. <https://doi.org/10.1007/s11547-020-01239-2>
- Nouh MR, Eid AF. Magnetic resonance imaging of the spinal marrow: basic understanding of the normal marrow pattern and its variant. *WJR* 2015; **7**: 448. <https://doi.org/10.4329/wjr.v7.i12.448>
- Laor T, Jaramillo D. MR imaging insights into skeletal maturation: what is normal? *Radiology* 2009; **250**: 28–38. <https://doi.org/10.1148/radiol.2501071322>
- Chan BY, Gill KG, Rebsamen SL, Nguyen JC. MR imaging of pediatric bone marrow. *Radiographics* 2016; **36**: 1911–30. <https://doi.org/10.1148/rg.2016160056>
- Bracken J, Nandurkar D, Radhakrishnan K, Ditchfield M. Normal paediatric bone marrow: magnetic resonance imaging appearances from birth to 5 years: MRI appearance of normal marrow from 0-5 years. *J Med Imaging Radiat Oncol* 2013; **57**: 283–91.
- Waitches G, Zawin JK, Poznanski AK. Sequence and rate of bone marrow conversion in the femora of children as seen on MR imaging: are accepted standards accurate? *AJR Am J Roentgenol* 1994; **162**: 1399–1406. <https://doi.org/10.2214/ajr.162.6.8192007>
- Hanrahan CJ, Shah LM. MRI of spinal bone marrow: part 2, T1-weighted imaging-based differential diagnosis. *AJR Am J Roentgenol* 2011; **197**: 1309–21. <https://doi.org/10.2214/AJR.11.7420>
- O'Hare A, Shortt C, Napier N, Eustace SJ. Bone marrow edema: patterns and clinical implications. *Semin Musculoskelet Radiol* 2006; **10**: 249–57. <https://doi.org/10.1055/s-2007-971996>
- Howe BM, Johnson GB, Wenger DE. Current concepts in MRI of focal and diffuse malignancy of bone marrow. *Semin Musculoskelet Radiol* 2013; **17**: 137–44. <https://doi.org/10.1055/s-0033-1343069>
- Carroll KW, Feller JE, Tirman PFJ. Useful internal standards for distinguishing infiltrative marrow pathology from hematopoietic marrow at MRI. *J Magn Reson Imaging* 1997; **7**: 394–98. <https://doi.org/10.1002/jmri.1880070224>
- Vande Berg BC, Lecouvet FE, Galant C, Simoni P, Malghem J. Normal variants of the bone marrow at MR imaging of the spine. *Semin Musculoskelet Radiol* 2009; **13**: 87–96. <https://doi.org/10.1055/s-0029-1220879>
- van Vucht N, Santiago R, Lottmann B, Pressney I, Harder D, Sheikh A, et al. The dixon technique for MRI of the bone marrow. *Skeletal Radiol* 2019; **48**: 1861–74. <https://doi.org/10.1007/s00256-019-03271-4>
- Pal CR, Tasker AD, Ostlere SJ, Watson MS. Heterogeneous signal in bone marrow on MRI of children's feet: a normal finding? *Skeletal Radiol* 1999; **28**: 274–78. <https://doi.org/10.1007/s002560050515>
- Shabshin N, Schweitzer ME, Morrison WB, Carrino JA, Keller MS, Grissom LE. High-signal T2 changes of the bone marrow of the foot and ankle in children: red marrow or traumatic changes? *Pediatr Radiol* 2006; **36**: 670–76. <https://doi.org/10.1007/s00247-006-0129-y>
- Zbojniec AM, Laor T. Focal periphyseal edema (fope) zone on MRI of the adolescent

- knee: A potentially painful manifestation of physiologic physeal fusion? *AJR Am J Roentgenol* 2011; **197**: 998–1004. <https://doi.org/10.2214/AJR.10.6243>
16. Giles E, Nicholson A, Sharkey MS, Carter CW. Focal periphyseal edema: are we overtreating physiologic adolescent knee pain? *J Am Acad Orthop Surg Glob Res Rev* 2018; **2**: e047. <https://doi.org/10.5435/JAAOSGlobal-D-17-00047>
 17. Małkiewicz A, Dziedzic M. Rekonwersja szpiku – obrazowanie fizjologicznych zmian szpiku w codziennej praktyce. *Pol J Radiol* 2012; **77**: 45–50. <https://doi.org/10.12659/PJR.883628>
 18. Vo MT, Singh A, Meng T, Kaur J, Venn A, Cicutini F, et al. Prevalence and clinical significance of residual or reconverted red bone marrow on knee MRI. *Diagnostics (Basel)* 2021; **11**(9): 1531. <https://doi.org/10.3390/diagnostics11091531>
 19. Gonzalez FM, Mitchell J, Monfred E, Anguh T, Mulligan M. Knee MRI patterns of bone marrow reconversion and relationship to anemia. *Acta Radiol* 2016; **57**: 964–70. <https://doi.org/10.1177/0284185115610932>
 20. Poulton TB, Murphy WD, Duerk JL, Chapek CC, Feiglin DH. Bone marrow reconversion in adults who are smokers: MR imaging findings. *AJR Am J Roentgenol* 1993; **161**: 1217–21. <https://doi.org/10.2214/ajr.161.6.8249729>
 21. Caldemeyer KS, Smith RR, Harris A, Williams T, Huang Y, Eckert GJ, et al. Hematopoietic bone marrow hyperplasia: correlation of spinal MR findings, hematologic parameters, and bone mineral density in endurance athletes. *Radiology* 1996; **198**: 503–8. <https://doi.org/10.1148/radiology.198.2.8596857>
 22. Pogodina VV. Elizaveta nilolaevna levkovich-75th birthday. *Acta Virol* 1975; **19**(6): 509.
 23. Cosentini T, Le Donne R, Mancini D, Aleandri AR, Colavita N. Magnetic resonance imaging evaluation of bone marrow changes in obstructive sleep apnoea syndrome in adults. *Radiol Med* 2006; **111**: 572–84. <https://doi.org/10.1007/s11547-006-0052-1>
 24. Gu L, Madewell JE, Aslam R, Mujtaba B. The effects of granulocyte colony-stimulating factor on MR images of bone marrow. *Skeletal Radiol* 2018; **48**: 209–18. <https://doi.org/10.1007/s00256-018-3035-0>
 25. Martinoli C, Bacigalupo L, Forni G, Balocco M, Garlaschi G, Tagliafico A. Musculoskeletal manifestations of chronic anemias. *Semin Musculoskelet Radiol* 2011; **15**: 269–80. <https://doi.org/10.1055/s-0031-1278426>
 26. Murphy IG, Mitchell EL, Raso-Barnett L, Godfrey AL, Godfrey EM. Imaging features of myeloproliferative neoplasms. *Clin Radiol* 2017; **72**: S0009-9260(17)30206-4: 801–9. <https://doi.org/10.1016/j.crad.2017.05.014>
 27. Liput J, Smith DA, Beck R, Ramaiya NH. Myeloproliferative neoplasms: A primer for radiologists. *J Comput Assist Tomogr* 2019; **43**: 652–63. <https://doi.org/10.1097/RCT.0000000000000893>
 28. Kwiatkowska-Pamula A, Ziółko E, Muc-Wierżgoń M, Nowakowska-Zajdel E, Podwińska E, Adamczyk T. Usefulness of spinal magnetic resonance imaging in patients with myelodysplastic syndromes. *Pol J Radiol* 2013; **78**: 42–49. <https://doi.org/10.12659/PJR.883766>
 29. Hajimoradi M, Haseli S, Abadi A, Chalian M. Musculoskeletal imaging manifestations of beta-thalassemia. *Skeletal Radiol* 2021; **50**: 1749–62. <https://doi.org/10.1007/s00256-021-03732-9>
 30. Kosaraju V, Harwani A, Partovi S, Bhojwani N, Garg V, Ayyappan S, et al. Imaging of musculoskeletal manifestations in sickle cell disease patients. *Br J Radiol* 2017; **90**(1073): 20160130. <https://doi.org/10.1259/bjr.20160130>
 31. Oon SF, Singh D, Tan TH, Lee A, Noe G, Burbury K, et al. Primary myelofibrosis: spectrum of imaging features and disease-related complications. *Insights Imaging* 2019; **10**(1): 71. <https://doi.org/10.1186/s13244-019-0758-y>
 32. Leone A, Criscuolo M, Gulli C, Petrosino A, Carlo Bianco N, Colosimo C. Systemic mastocytosis revisited with an emphasis on skeletal manifestations. *Radiol Med* 2021; **126**: 585–98. <https://doi.org/10.1007/s11547-020-01306-8>
 33. Riffel P, Jawhar M, Gawlik K, Schwaab J, Michaely HJ, Metzgeroth G, et al. Magnetic resonance imaging reveals distinct bone marrow patterns in indolent and advanced systemic mastocytosis. *Ann Hematol* 2019; **98**: 2693–2701. <https://doi.org/10.1007/s00277-019-03826-4>
 34. Vande Berg BC, Kirchgessner T, Acid S, Malghem J, Vekemans MC, Lecouvet FE. Diffuse vertebral marrow changes at MRI: multiple myeloma or normal? *Skeletal Radiol* 2022; **51**: 89–99. <https://doi.org/10.1007/s00256-021-03886-6>
 35. Pawlyn C, Fowkes L, Otero S, Jones JR, Boyd KD, Davies FE, et al. Whole-body diffusion-weighted MRI: a new gold standard for assessing disease burden in patients with multiple myeloma? *Leukemia* 2016; **30**: 1446–48. <https://doi.org/10.1038/leu.2015.338>
 36. Shah GL, Rosenberg AS, Jarboe J, Klein A, Cossor F. Incidence and evaluation of incidental abnormal bone marrow signal on magnetic resonance imaging. *ScientificWorldJournal* 2014; **2014**: 380814: 1–6. <https://doi.org/10.1155/2014/380814>
 37. Carlson HL, Thompson AR, Pettersson DR, Goodwin B, Deloughery TG, Carlson NL, et al. Prevalence and clinical significance of incidental vertebral marrow signal abnormality in thoracolumbar spine MRI. *Spine (Phila Pa 1976)* 2020; **45**: 390–96. <https://doi.org/10.1097/BRS.0000000000003278>
 38. Rajakulasingam R, Saifuddin A. Focal nodular marrow hyperplasia: imaging features of 53 cases. *Br J Radiol* 2020; **93**(1112): 20200206. <https://doi.org/10.1259/bjr.20200206>
 39. Bordalo-Rodrigues M, Galant C, Lonnew M, Clause D, Vande Berg BC. Focal nodular hyperplasia of the hematopoietic marrow simulating vertebral metastasis on FDG positron emission tomography. *AJR Am J Roentgenol* 2003; **180**: 669–71. <https://doi.org/10.2214/ajr.180.3.1800669>
 40. Shigematsu Y, Hirai T, Kawanaka K, Shiraishi S, Yoshida M, Kitajima M, et al. Distinguishing imaging features between spinal hyperplastic hematopoietic bone marrow and bone metastasis. *AJNR Am J Neuroradiol* 2014; **35**: 2013–20. <https://doi.org/10.3174/ajnr.A4012>
 41. Suh CH, Yun SJ, Jin W, Park SY, Ryu C-W, Lee SH. Diagnostic performance of in-phase and opposed-phase chemical-shift imaging for differentiating benign and malignant vertebral marrow lesions: A meta-analysis. *AJR Am J Roentgenol* 2018; **211**: W188–97. <https://doi.org/10.2214/AJR.17.19306>
 42. Oki N, Ikebe Y, Koike H, Ideguchi R, Niino D, Uetani M. FDG-PET vs. chemical shift MR imaging in differentiating intertrabecular metastasis from hematopoietic bone marrow hyperplasia. *Jpn J Radiol* 2021; **39**: 1077–85. <https://doi.org/10.1007/s11604-021-01149-x>
 43. Park S, Kwack K-S, Chung N-S, Hwang J, Lee HY, Kim JH. Intravoxel incoherent motion diffusion-weighted magnetic resonance imaging of focal vertebral bone marrow lesions: initial experience of the differentiation of nodular hyperplastic hematopoietic bone marrow from malignant lesions. *Skeletal Radiol* 2017; **46**: 675–83. <https://doi.org/10.1007/s00256-017-2603-z>
 44. Kwack K-S, Lee H-D, Jeon SW, Lee HY, Park S. Comparison of proton density fat fraction, simultaneous R2*, and apparent diffusion coefficient for assessment of focal vertebral bone marrow lesions. *Clin Radiol* 2020; **75**:

- S0009-9260(19)30589-6: 123–30. . <https://doi.org/10.1016/j.crad.2019.09.141>
45. Schmeel FC, Enkirch SJ, Luetkens JA, Faron A, Lehnen N, Sprinkart AM, et al. Diagnostic accuracy of quantitative imaging biomarkers in the differentiation of benign and malignant vertebral lesions : combination of diffusion-weighted and proton density fat fraction spine MRI. *Clin Neuroradiol* 2021; **31**: 1059–70. <https://doi.org/10.1007/s00062-021-01009-1>
 46. van Vucht N, Santiago R, Pressney I, Saifuddin A. Role of in-phase and out-of-phase chemical shift MRI in differentiation of non-neoplastic versus neoplastic benign and malignant marrow lesions. *Br J Radiol* 2021; **94**(1119): 20200710. <https://doi.org/10.1259/bjr.20200710>
 47. van Vucht N, Santiago R, Pressney I, Saifuddin A. Anomalous signal intensity increase on out-of-phase chemical shift imaging: a manifestation of marrow mineralisation? *Skeletal Radiol* 2020; **49**: 1269–75. <https://doi.org/10.1007/s00256-020-03420-0>
 48. Saifuddin A, Shafiq H, Malhotra K, Santiago R, Pressney I. Comparison of in-phase and opposed-phase T1W gradient echo and T2W fast spin echo dixon chemical shift imaging for the assessment of non-neoplastic, benign neoplastic and malignant marrow lesions. *Skeletal Radiol* 2021; **50**: 1209–18. <https://doi.org/10.1007/s00256-020-03663-x>
 49. Schweitzer ME, Levine C, Mitchell DG, Gannon FH, Gomella LG. Bull's-eyes and halos: useful MR discriminators of osseous metastases. *Radiology* 1993; **188**: 249–52. <https://doi.org/10.1148/radiology.188.1.8511306>
 50. Saifuddin A, Sharif B, Oliveira I, Kalus S, Barnett J, Pressney I. The incidence of skip metastases on whole bone MRI in high-grade bone sarcomas. *Skeletal Radiol* 2020; **49**: 945–54. <https://doi.org/10.1007/s00256-019-03369-9>
 51. Chow LTC, Ng AWH, Wong SKC. Focal nodular and diffuse haematopoietic marrow hyperplasia in patients with underlying malignancies: a radiological mimic of malignancy in need of recognition. *Clin Radiol* 2017; **72**: S0009-9260(16)30438-X: 265. . <https://doi.org/10.1016/j.crad.2016.10.015>
 52. Maraghelli D, Brandi ML, Matucci Cerinic M, Peired AJ, Colagrande S. Edema-like marrow signal intensity: a narrative review with a pictorial essay. *Skeletal Radiol* 2021; **50**: 645–63. <https://doi.org/10.1007/s00256-020-03632-4>
 53. Gil HC, Levine SM, Zoga AC. MRI findings in the subchondral bone marrow: A discussion of conditions including transient osteoporosis, transient bone marrow edema syndrome, SONK, and shifting bone marrow edema of the knee. *Semin Musculoskelet Radiol* 2006; **10**: 177–86. <https://doi.org/10.1055/s-2006-957171>
 54. Thawait SK, Marcus MA, Morrison WB, Klufas RA, Eng J, Carrino JA. Research synthesis: what is the diagnostic performance of magnetic resonance imaging to discriminate benign from malignant vertebral compression fractures? systematic review and meta-analysis. *Spine (Phila Pa 1976)* 2012; **37**: E736-44. <https://doi.org/10.1097/BRS.0b013e3182458cac>
 55. Schmeel FC, Luetkens JA, Enkirch SJ, Feißt A, Endler CH-J, Schmeel LC, et al. Proton density fat fraction (PDFF) MR imaging for differentiation of acute benign and neoplastic compression fractures of the spine. *Eur Radiol* 2018; **28**: 5001–9. <https://doi.org/10.1007/s00330-018-5513-0>
 56. Schmeel FC, Luetkens JA, Feißt A, Enkirch SJ, Endler CH-J, Wagenhäuser PJ, et al. Quantitative evaluation of T2* relaxation times for the differentiation of acute benign and malignant vertebral body fractures. *Eur J Radiol* 2018; **108**: S0720-048X(18)30325-5: 59–65. . <https://doi.org/10.1016/j.ejrad.2018.09.021>
 57. Bacher S, Hajdu SD, Maeder Y, Dunet V, Hilbert T, Omoumi P. Differentiation between benign and malignant vertebral compression fractures using qualitative and quantitative analysis of a single fast spin echo T2-weighted dixon sequence. *Eur Radiol* 2021; **31**: 9418–27. <https://doi.org/10.1007/s00330-021-07947-1>
 58. Suh CH, Yun SJ, Jin W, Lee SH, Park SY, Ryu C-W. ADC as a useful diagnostic tool for differentiating benign and malignant vertebral bone marrow lesions and compression fractures: a systematic review and meta-analysis. *Eur Radiol* 2018; **28**: 2890–2902. <https://doi.org/10.1007/s00330-018-5330-5>
 59. Marshall RA, Mandell JC, Weaver MJ, Ferrone M, Sodickson A, Khurana B. Imaging features and management of stress, atypical, and pathologic fractures. *Radiographics* 2018; **38**: 2173–92. <https://doi.org/10.1148/rg.2018180073>
 60. Zhong X, Dong T, Tan Y, Li J, Mai H, Wu S, et al. Pelvic insufficiency fracture or bone metastasis after radiotherapy for cervical cancer? the added value of DWI for characterization. *Eur Radiol* 2020; **30**: 1885–95. <https://doi.org/10.1007/s00330-019-06520-1>
 61. Lee S, Saifuddin A. Magnetic resonance imaging of subchondral insufficiency fractures of the lower limb. *Skeletal Radiol* 2019; **48**: 1011–21. <https://doi.org/10.1007/s00256-019-3160-4>
 62. Larsen MS, Schmal H. The enigma of atypical femoral fractures: A summary of current knowledge. *EFORT Open Rev* 2018; **3**: 494–500. <https://doi.org/10.1302/2058-5241.3.170070>
 63. Png MA, Koh JSB, Goh SK, Fook-Chong S, Howe TS. Bisphosphonate-related femoral periosteal stress reactions: scoring system based on radiographic and MRI findings. *AJR Am J Roentgenol* 2012; **198**: 869–77. <https://doi.org/10.2214/AJR.11.6794>
 64. Fayad LM, Kamel IR, Kawamoto S, Bluemke DA, Frassica FJ, Fishman EK. Distinguishing stress fractures from pathologic fractures: a multimodality approach. *Skeletal Radiol* 2005; **34**: 245–59. <https://doi.org/10.1007/s00256-004-0872-9>
 65. Chaib B, Malhotra K, Khoo M, Saifuddin A. Pathological fracture in paediatric bone tumours and tumour-like lesions: A predictor of benign lesions? *Br J Radiol* 2021; **94**(1125): 20201341. <https://doi.org/10.1259/bjr.20201341>
 66. Lunkiewicz M, Anderson S, Havakeshian S, Würzburg A. Practical input on bone tumor imaging: pathological fracture, risk features, and when to contact orthopaedics. *Semin Musculoskelet Radiol* 2019; **23**: 019–025. <https://doi.org/10.1055/s-0038-1675804>
 67. Fayad LM, Kawamoto S, Kamel IR, Bluemke DA, Eng J, Frassica FJ, et al. Distinction of long bone stress fractures from pathologic fractures on cross-sectional imaging: how successful are we? *AJR Am J Roentgenol* 2005; **185**: 915–24. <https://doi.org/10.2214/AJR.04.0950>
 68. James SLJ, Hughes RJ, Ali KE, Saifuddin A. MRI of bone marrow oedema associated with focal bone lesions. *Clin Radiol* 2006; **61**: 1003–9. <https://doi.org/10.1016/j.crad.2006.07.007>
 69. James SLJ, Panicek DM, Davies AM. Bone marrow oedema associated with benign and malignant bone tumours. *Eur J Radiol* 2008; **67**: 11–21. <https://doi.org/10.1016/j.ejrad.2008.01.052>
 70. Gao S, Zhou R, Xu Q, Chen H. Edema surrounding benign tumors and tumor-like lesions. *Biomed Res Int* 2019; **2019**: 8206913: 1–7. . <https://doi.org/10.1155/2019/8206913>
 71. Carneiro BC, Da Cruz IAN, Ormond Filho AG, Silva IP, Guimarães JB, Silva FD, et al. Osteoid osteoma: the great mimicker. *Insights Imaging* 2021; **12**(1): 32. <https://doi.org/10.1186/s13244-021-00978-8>
 72. Saifuddin A, Santiago R, van Vucht N, Pressney I. Comparison of T1-weighted turbo spin echo and out-of-phase T1-

- weighted gradient echo dixon MRI for the assessment of intra-medullary length of appendicular bone tumours. *Skeletal Radiol* 2021; **50**: 993–1005. <https://doi.org/10.1007/s00256-020-03654-y>
73. Desimpel J, Posadzy M, Vanhoenacker F. The many faces of osteomyelitis: A pictorial review. *J Belg Soc Radiol* 2017; **101**: 24. <https://doi.org/10.5334/jbr-btr.1300>
 74. van der Naald N, Smeeing DPJ, Houwert RM, Hietbrink F, Govaert GAM, van der Velde D. Brodie's abscess: A systematic review of reported cases. *J Bone Jt Infect* 2019; **4**: 33–39. <https://doi.org/10.7150/jbji.31843>
 75. Davies AM, Hughes DE, Grimer RJ. Intramedullary and extramedullary fat globules on magnetic resonance imaging as a diagnostic sign for osteomyelitis. *Eur Radiol* 2005; **15**: 2194–99. <https://doi.org/10.1007/s00330-005-2771-4>
 76. McGuinness B, Wilson N, Doyle AJ. The “penumbra sign” on T1-weighted MRI for differentiating musculoskeletal infection from tumour. *Skeletal Radiol* 2007; **36**: 417–21. <https://doi.org/10.1007/s00256-006-0267-1>
 77. Shimose S, Sugita T, Kubo T, Matsuo T, Nobuto H, Ochi M. Differential diagnosis between osteomyelitis and bone tumors. *Acta Radiol* 2008; **49**: 928–33. <https://doi.org/10.1080/02841850802241809>
 78. Sardana R, Sardana NK, Sharma A. Tuberculosis of the axial skeleton mimicking malignancy. *J R Coll Physicians Edinb* 2020; **50**: 168–70. <https://doi.org/10.4997/JRCPE.2020.221>
 79. Jurik AG, Klicman RF, Simoni P, Robinson P, Teh J. SAPHO and CRMO: the value of imaging. *Semin Musculoskelet Radiol* 2018; **22**: 207–24. <https://doi.org/10.1055/s-0038-1639469>
 80. Laredo J-D, Vuillemin-Bodaghi V, Boutry N, Cotten A, Parlier-Cuau C. SAPHO syndrome: MR appearance of vertebral involvement. *Radiology* 2007; **242**: 825–31. <https://doi.org/10.1148/radiol.2423051222>
 81. Leone A, Cassar-Pullicino VN, Casale R, Magarelli N, Semprini A, Colosimo C. The SAPHO syndrome revisited with an emphasis on spinal manifestations. *Skeletal Radiol* 2015; **44**: 9–24. <https://doi.org/10.1007/s00256-014-2025-0>
 82. Xu W, Li C, Zhao X, Lu J, Li L, Wu N, et al. Whole-spine computed tomography findings in SAPHO syndrome. *J Rheumatol* 2017; **44**: 648–54. <https://doi.org/10.3899/jrheum.161075>
 83. d'Angelo P, de Horatio LT, Toma P, Ording Müller L-S, Avenarius D, von Brandis E, et al. Chronic nonbacterial osteomyelitis - clinical and magnetic resonance imaging features. *Pediatr Radiol* 2021; **51**: 282–88. <https://doi.org/10.1007/s00247-020-04827-6>
 84. Vilanova JC, García-Figueiras R, Luna A, Baleato-González S, Tomás X, Narváez JA. Update on whole-body MRI in musculoskeletal applications. *Semin Musculoskelet Radiol* 2019; **23**: 312–23. <https://doi.org/10.1055/s-0039-1685540>
 85. Andronikou S, Mendes da Costa T, Hussien M, Ramanan AV. Radiological diagnosis of chronic recurrent multifocal osteomyelitis using whole-body MRI-based lesion distribution patterns. *Clin Radiol* 2019; **74**: S0009-9260(19)30267-3: 737. <https://doi.org/10.1016/j.crad.2019.02.021>
 86. Suresh S, Saifuddin A. Unveiling the “unique bone”: a study of the distribution of focal clavicular lesions. *Skeletal Radiol* 2008; **37**: 749–56. <https://doi.org/10.1007/s00256-008-0507-7>
 87. Clement ND, Nyadu Y, Kelly M, Walmsley P, Porter DE. Malignant lesions are rare in medial third of the clavicle in children: the european juvenile medial end of clavicle tumour study. *J Pediatr Orthop B* 2011; **20**: 117–23. <https://doi.org/10.1097/BPB.0b013e328344107a>
 88. Hirji H, Saifuddin A. Paediatric acquired pathological vertebral collapse. *Skeletal Radiol* 2014; **43**: 423–36. <https://doi.org/10.1007/s00256-013-1792-3>
 89. Hara H, Akisue T, Fujimoto T, Kishimoto K, Imabori M, Kishimoto S, et al. Magnetic resonance imaging of medullary bone infarction in the early stage. *Clin Imaging* 2008; **32**: 147–51. <https://doi.org/10.1016/j.clinimag.2007.07.005>
 90. Barakat E, Guischer N, Houssiau F, Lecouvet FE. The “birth of death”: MRI step-by-step reveals the early appearance of a bone marrow infarct. *Acta Radiol Open* 2019; **8**: 2058460119834691. <https://doi.org/10.1177/2058460119834691>
 91. Fowler NO, McCall D, Chou TC, Holmes JC, Hanenson IB. Electrocardiographic changes and cardiac arrhythmias in patients receiving psychotropic drugs. *The American Journal of Cardiology* 1976; **37**: 223–30. [https://doi.org/10.1016/0002-9149\(76\)90316-7](https://doi.org/10.1016/0002-9149(76)90316-7)
 92. Boutin RD, White LM, Laor T, Spitz DJ, Lopez-Ben RR, Stevens KJ, et al. MRI findings of serous atrophy of bone marrow and associated complications. *Eur Radiol* 2015; **25**: 2771–78. <https://doi.org/10.1007/s00330-015-3692-5>
 93. Mondal M, Gaba S. “Flip-flop phenomenon” - magnetic resonance imaging pitfall: A case report. *Radiology Case* 2021; **15**: 19–25. <https://doi.org/10.3941/jrcr.v15i6.4271>
 94. Kalamar V, Davies A, Wright P, Suresh P. MRI findings seen in serous atrophy of bone marrow. *BMJ Case Rep* 2021; **14**: e243770. <https://doi.org/10.1136/bcr-2021-243770>