# "Flip-Flop Phenomenon" - Magnetic Resonance Imaging Pitfall: A Case Report

Monojit Mondal[1*], Suchi Gaba[2]

*1. Department of Clinical Radiology, Ysbyty Gwynedd Hospital; Penrhosgarnedd, Bangor, Gwynedd, United Kingdom*

*2. Department of Clinical Radiology, Royal Stoke University Hospital; Stoke-on-Trent, United Kingdom*

* **Correspondence:** Monojit Mondal, Department of Clinical Radiology, Ysbyty Gwynedd, Penrhosgarnedd, Bangor, Gwynedd, LL57 2PW, United Kingdom
(*Monojit.Mondal@wales.nhs.uk*)

Radiology Case. 2021 Jun; 15(6):19-25 :: DOI: 10.3941/jrcr.v15i6.4271

ABSTRACT

A 66-year-old cachectic female with underlying anorexia nervosa and lower limb weakness was referred for a spinal Magnetic Resonance Imaging. Imaging appearances were initially thought to represent underlying systemic pathology involving bone marrow or inadvertent wrong selection of imaging sequences. It was, however, established that unique imaging appearances are secondary to 'Flip-Flop' phenomenon owing to underlying nutritional status of the patient. 'Flip-Flop' phenomenon on the Magnetic Resonance Imaging is result of an underlying pathological process of serous atrophy of bone marrow. Appreciation and recognition of this phenomenon will help in the correct interpretation of the images and leads a clinician toward appropriate management.





## CASE REPORT

### CASE REPORT

A 66-year-old cachectic female presented to the emergency department with increasing confusion, memory problems, muscle weakness and wasting in the lower limb. She was known to have anorexia nervosa and hypothyroidism.

The patient was investigated for muscle weakness in the lower limbs. A thorough neurological examination found that she had increased tone and power of 4/5 in bilateral lower limbs and wasting in all muscle groups, however, reflexes were normal and had no altered sensations. There was no loss or alteration of perianal sensation. Blood investigations revealed the serum sodium to be as low as 118 mmol/L (normal range 133-146), low albumin of 30 g/L (normal range 35-50), and low plasma osmolality 251mosm/kg (normal range 285-295). She was further investigated with Magnetic Resonance Imaging (MRI) of the whole spine, electromyography and nerve conduction studies.

A whole spine MRI was performed to rule out any neurological pathology to account for the symptoms. Initial MRI of the whole spine was done on Siemens 1.5 T MRI scanner (Aera®).

The T1 weighted sagittal sequence images (Fig. 1A) were grossly abnormal. It appeared that fat saturation sequences was inadvertently selected whilst obtaining these images. The images revealed homogenous signal suppression of fatty bone marrow and subcutaneous fat in the whole spine. The T2 weighted sagittal images (Fig. 1B) revealed heterogenous variegated marrow signal, however, the spinal cord and cauda equina nerve roots were normal. The initial interpretation of the MRI was thought to be either a manifestation of systemic

pathology with a diffuse infiltrative pattern in the bone marrow or possible equipment malfunction/ inappropriate selection of sequences.

Owing to a concern of an underlying infiltrative disorder, the patient was recalled for a repeat MRI spine on a 3 Tesla Siemens MRI scanner (VIDA®). The T1W (Fig. 2A) and Short-Tau Inversion Recovery (STIR) weighted sequences (Fig. 2B) were again acquired on this scanner, and these reproduced the same imaging pattern noted earlier on 1.5T scanner. There was no difference in images acquired with or without fat saturation obtained on both the scanners. The T1W images were similar despite the manual selection of the MR parameters and frequency adjustment. The T1W sequences revealed diffuse hypointensity throughout whole of the imaged spine (Fig. 2C). Fluid sensitive STIR sequences (Fig. 2B) showed heterogeneous bone marrow, which appeared as hyperintense (bright) due to incomplete suppression suggesting edema or infiltration.

Contrast-enhanced Computed Tomography (CECT) of chest, abdomen, and pelvis revealed no mass lesion or lymphadenopathy, however, there was non-visualization of subcutaneous and intra-abdominal fat (Fig. 3A and 3B).

Furthermore, the lumbar spine MRI performed 10 years before the current presentation, revealed normal appearances of bone marrow and subcutaneous fat on both T1 and T2 W images (Fig 4A, 4B).

From the neurology standpoint, the EMG studies did not support an anterior horn cell disorder. The nerve conduction studies in bilateral lower limbs suggested a mild sensorimotor axonal peripheral neuropathy affecting mainly sensory nerves.

Initial suspicion of inadvertent improper sequence selection was ruled out and attention was paid to the patient's relevant prior clinical history, discussion with the clinicians regarding atypical imaging pattern, and further literature search were performed. It was deduced that there was severe depletion of fat stores in the body and hence there were ensuing changes in the bone marrow.

The patient was discharged following an inpatient stay and is being followed up in an outpatient setting by an eating disorder and memory teams. On further follow up of 8 months, there is no clinical deterioration in patient's symptoms, however, the patient still suffers from perennial low mood and significantly reduced appetite suggesting ongoing underlying psychiatric issues.

## DISCUSSION

*Etiology & Demographics:*

The demographics for 'serous atrophy of bone marrow' (SABM) also called as gelatinous transformation of bone marrow causing the imaging manifestation known as 'Flip-Flop' is heterogeneous. It is generally seen in adults, more often in male patients. It has bimodal age distribution, with young adults as the first age group that is related to underlying conditions like anorexia nervosa or Acquired immune deficiency syndrome (AIDS). The second age bracket are people in their sixth decade and older with systemic disorders like cancer-induced cachexia and chronic heart failure [1]. The reported incidence varies, however, the largest pathological series suggests it to be approximately 0.2% [2].

Gelatinous transformation of bone marrow is not a disease entity in itself, however, it is a benign manifestation of the underlying chronic disease with ensuing catabolic state causing progressive depletion of initially fat and subsequently protein stores from the body that results in chronically deprived nutrition to the fatty marrow. There is a gradual replacement of fatty marrow by acid mucopolysaccharides, which is hyaluronic acids [3].

*Clinical and imaging findings:*

The clinical condition reflects the poor nutritional status of the patient apparent by the fact that 80% of patients with 'SABM' have anemia and significant weight loss [1].

The characteristic MRI findings aid towards correct interpretation of the imaging, if the clinical details are put into context as shown in this case. There is striking diffuse hypointensity of bone marrow on T1 W images, hyperintensity on T2 W images and fluid sensitive STIR sequences reflecting the increase in water content which might trick the radiologist/clinician and erroneously lead towards suspicion of an underlying sinister neoplastic disorder like metastatic disease [3]. These characteristic signal changes of the bone marrow with non-visualisation of fatty marrow on T1W images and apparent lack of fat saturation in sequences like STIR is known as 'flip-flop' effect [4]. Owing to the universal depletion of fat stores, there is a paucity of subcutaneous and visceral fat that is noticed on different imaging modalities [3].

This phenomenon which is due to abundance of water and almost complete absence of fat stores in the bone marrow and subcutaneous region can be confirmed by MR spectroscopy, if required. Dixon technique commonly used for differentiating between fat and water may also be utilized and will demonstrate the absence of fat [4].

Another common skeletal manifestation seen in this cohort of patients is stress fractures due to a combination of osteopenia and altered bone composition. The MRI diagnosis can be challenging in these patients due to inherent signal abnormalities masking the marrow edema from the fracture. Often the radiologist has to have a high index of suspicion to raise the possibility. A CT scan might help to diagnose such fractures [5].

*Treatment & Prognosis:*

The primary motive in treatment is to address an underlying systemic condition responsible for poor nutritional status. If associated with anorexia nervosa, then nutritional support is mandatory with psychiatric evaluation and treatment. Hematopoietic growth factors might help in recalcitrant cases [6].

It has been shown that severe serous atrophy of the bone marrow is reversible with nutritional intervention, however, it requires sustained effort on the part of the clinical teams [7].

*Differential Diagnosis:*

The main differential diagnosis for this imaging pattern is pathological marrow infiltrative disorder like metastases, leukemia, multiple myeloma, and lymphoma [3,7,8]. These neoplastic conditions typically present with weakness, weight loss, and back pain similar to the clinical presentation in this case causing clinical confusion. However, the marrow changes associated with conditions like metastases, myeloma appear initially in axial skeleton (spine and pelvis). Another feature of contrast in these highly divergent conditions is that in SABM the T2 W images of vertebral marrow often appears as heterogeneous, whereas neoplastic infiltration often appears as homogenous hyperintensity of axial skeleton [3].

Hematopoietic Hyperplasia is a condition where there is an exaggerated process of fatty marrow metamorphosis to red marrow when the capacity of the existing red marrow is superseded. This condition can be seen as a physiological process in athletes or can be observed in association with conditions like heavy smoking, chronic illnesses, and obesity. The pattern is similar to what is seen in pathological marrow conversion and starts in the axial skeleton like spine. MRI reveals patchy T1 hypointensity of vertebral bodies which is comparatively hyperintense to adjacent muscle/ intervertebral discs in contrast to diffuse processes like metastasis where hypointensity on T1 is significantly lower in signal intensity than that of muscle [9].

Myelofibrosis is a rare pathological process whereby normal marrow is gradually replaced by fibrotic tissue thus resulting in anemia and associated extramedullary hematopoiesis to compensate for the hypo functioning bone marrow. It could be primary in origin or can be secondary to chemo or radiotherapy. The MRI characteristically shows significant hypo intense signal on both T1W and T2 W images [9]. It is often accompanied with splenomegaly and other sites of extramedullary hematopoiesis commonly in paravertebral region [10].

Gaucher Disease is the most common lysosomal storage disease due to deficiency of glucocerebrosidase or beta-glucosidase enzyme causing accumulation of glucosylceramide in the reticuloendothelial system of the bone marrow, spleen, and liver. It commonly presents with anemia and thrombocytopenia with associated hepatosplenomegaly. Marrow infiltration initially involves the axial skeleton and then the peripheral skeleton. MRI of the bone marrow reveals hypointensity on both T1W and T2 W images. There is minimal hyperintensity on STIR, however significantly high signal on fluid sensitive sequences suggest underlying infection or infarction. Common associations are H shaped vertebrae, osteonecrosis in long bones and Erlenmeyer flask deformity of the distal femur [11].

## TEACHING POINT

'Flip-Flop' is a unique imaging manifestation in MRI resulting from the underlying pathological process of serous atrophy of bone marrow. It is seen generally in patients with poor nutritional status and low stores of body fat. The MRI findings in serous atrophy of bone marrow are uncommon, and to an unsuspecting radiologist and clinician, it might masquerade as generalized marrow infiltrative disorder thus potentially misdirecting the patient management. History of chronic illness or eating disorder along with significant paucity of adjacent subcutaneous fat on imaging should prompt the radiologist to this phenomenon. The radiologist should also carefully screen for insufficiency fractures which are difficult to identify but are not uncommon in these patients.

## REFERENCES

1. Böhm J. Gelatinous transformation of the bone marrow: the spectrum of underlying diseases. Am J Surg Pathol. 2000 Jan;24(1):56-65. PMID: 10632488

2. Shergill KK, Shergill GS, and Pillai HJ. Gelatinous transformation of bone marrow: rare or underdiagnosed?. Autops Case Rep. 2017 Oct-Dec;7(4):8-17. PMID: 29259927

3. Lee J, Yoo YH, Lee S, Kim HS, Kim S. Gelatinous Transformation of Bone Marrow Mimicking Malignant Marrow-Replacing Lesion on Magnetic Resonance Imaging in a Patient without Underlying Devastating Disease. iMRI 2018 March;22(1):50-55.

4. DiVasta AD, Mulkern RV, Gordon CM, Kirsten E. MR Imaging in a case of severe anorexia nervosa: the 'flip-flop' effect. Pediatr Radiol. 2015 Apr;45(4):617-620. PMID: 25129340

5. Tins B, Cassar- Pullicino V. Marrow changes in anorexia nervosa masking the presence of stress fractures on MR imaging. Skeletal Radiol.2006 Nov;35(11):857-60.DOI: 10.1007/s00256-005-0053-5.PMID 16308715

6. Tonogai I, Nakajima D, Miyagi R, Sairyo K. Gelatinous Transformation of Bone Marrow in the Calcaneus, Diagnosed by Open Bone Biopsy in a Patient With Anorexia Nervosa: A Case Report. Foot & Ankle Orthopaedics 2018 August;3(3). DOI: 10.1177/2473011418780325.

7. Steinberg SE, Nasraway S, Peterson L. Reversal of severe serous atrophy of the bone marrow in anorexia nervosa. JPEN J Parenter Enteral Nutr. 1987 Jul-Aug;11(4):422-3. DOI: 10.1177/0148607187011004422. PMID: 3112434

8. Hanrahan CJ, Shah LM. MRI of spinal bone marrow: part 2, T1-weighted imaging-based differential diagnosis. AJR Am J Roentgenol. 2011 Dec;197(6):1309-21. DOI:10.2214/AJR.11.7420.PMID:22109284

9. Christopher J. Hanrahan and Lubdha M. Shah. MRI of Spinal Bone Marrow: Part 2, T1-Weighted Imaging-Based Differential Diagnosis. American Journal of Roentgenology.

2011;197:1309-1321. DOI: 10.2214/AJR.11.7420. PMID: 22109284

10. Oon SF, Singh D, Tan TH et al. Primary myelofibrosis: spectrum of imaging features and disease-related complications. Insight Imaging. 2019 Aug7;10(1):71. DOI:10.1186/s13244-019-0758-y. PMID:31388788

11. Simpson William L, Hermann George, Balwani Manisha. Imaging of Gaucher disease. World J Radiol. 2014 Sep 28; 6(9): 657-668. DOI: 10.4329/wjr.v6.i9.657. PMID: 25276309

FIGURES

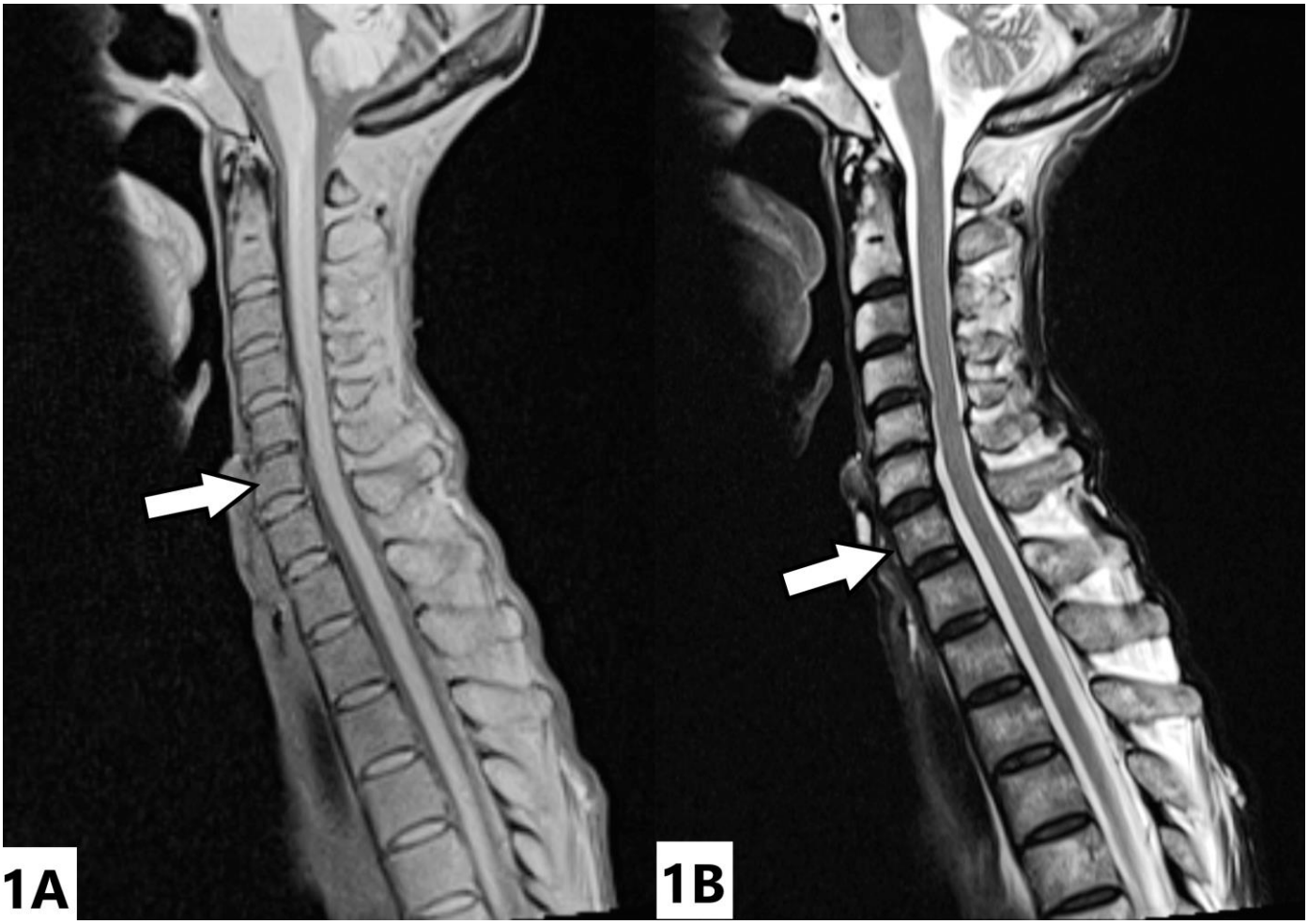


**Figure 1:** A 66-year-old female with flip-flop phenomenon - MRI pitfall.

FINDINGS: Initial MRI of the cervical spine, Fig 1(A) T1W image demonstrates homogenous hypointensity of bone marrow and non-visualisation of subcutaneous fat. Fig 1(B) T2W image shows variegated bone marrow signal.

TECHNIQUE: Siemens AERA MRI scanner. Magnetic strength 1.5 Tesla.
A. Sagittal T1-weighted, TR- 569, TE- 11, slice thickness- 3.0 mm
B. Sagittal T2-weighted, TR- 3650, TE- 104, slice thickness- 3.0 mm

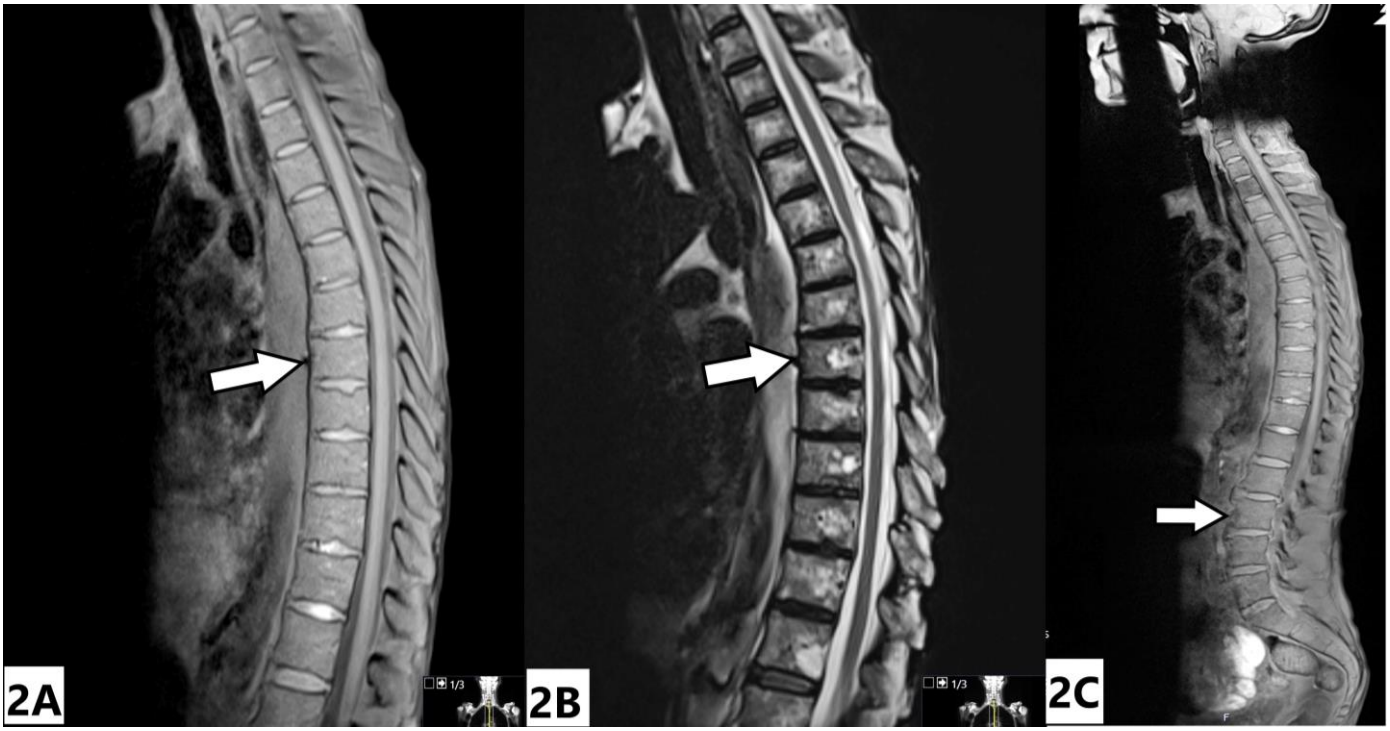


**Figure 2:** A 66-year-old female with flip-flop phenomenon - MRI pitfall.

FINDINGS: MRI of the dorsal and whole spine on a 3T MRI scanner with similar findings as seen with 1.5T scanner images as seen in Fig 1(A) and 1(B). Fig 2(A) T1W image demonstrates homogenous hypointensity of bone marrow and non visualisation of subcutaneous fat. Fig 2(B) Fluid sensitive STIR sequence showing incomplete signal suppression of marrow and subcutaneous fat simulating edema. Fig 2(C) Whole spine T1W image show hypointense bone marrow with no regional difference in the entire spine.

TECHNIQUE: Siemens VIDA MRI scanner. Magnetic strength 3 Tesla.
A. Sagittal T1-weighted, TR- 600, TE- 9.5, slice thickness- 3.0 mm
B. Sagittal STIR-weighted, TR- 4000, TE- 93, TI- 200, slice thickness- 3.0 mm
C. Sagittal T1-weighted, TR- 600, TE- 9.5, slice thickness- 3.0 mm

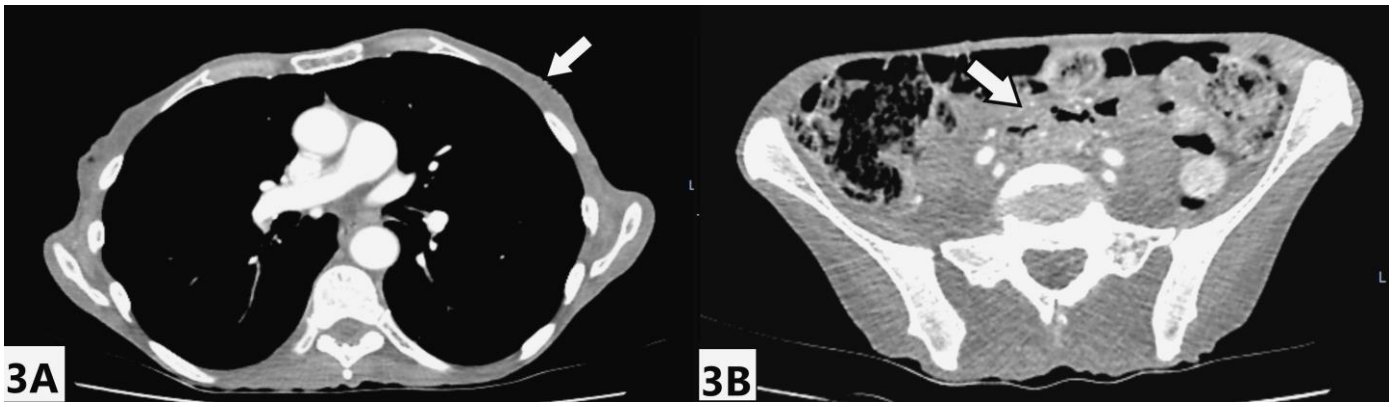


**Figure 3:** A 66-year-old female with flip-flop phenomenon - MRI pitfall.

FINDINGS: Contrast-Enhanced CT of the Chest 3(A) and Abdomen 3(B) demonstrate non-visualisation of subcutaneous, mesenteric and omental fat.

TECHNIQUE: Contrast enhanced CT of Chest, Abdomen and Pelvis, Toshiba Aquilion one CT scanner 320 detectors, 75 ml Omnipaque 300.
A: Axial, Arterial phase of the chest, 100 kV, 80 mA, slice thickness- 1.0 mm.
B: Axial, portal venous phase of the abdomen, 100 kV, 100 mA, slice thickness- 1.0 mm.

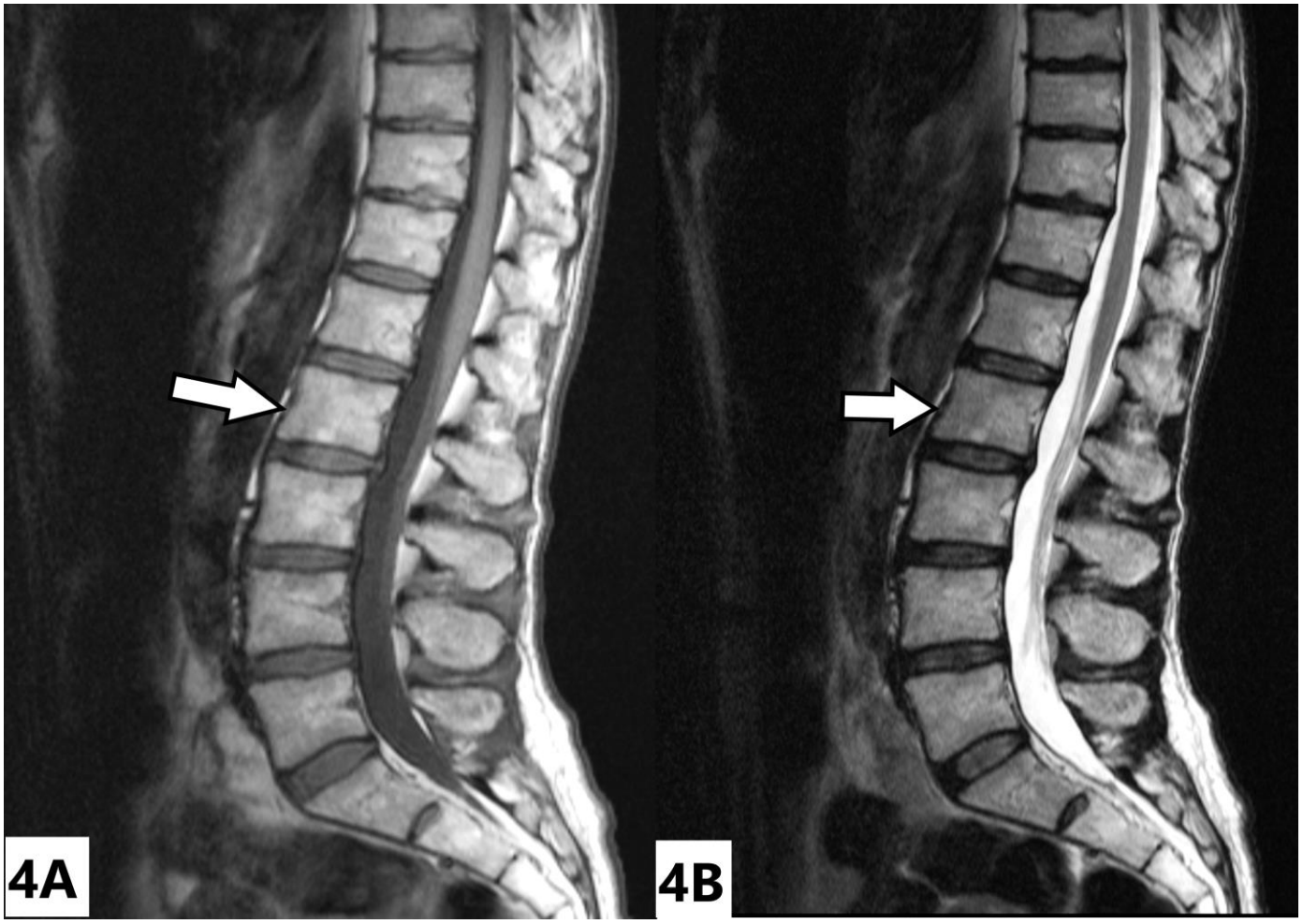


**Figure 4:** A 66-year-old female with flip-flop phenomenon - MRI pitfall.

FINDINGS: MRI of the Lumbar spine done 10 years before current presenation shows normal fatty bone marrow appearing hyperintense on both T1W Fig 4(A) and T2W images Fig 4(B), with demonstration of adequate subcutaneous fat.

TECHNIQUE: Siemens Symphony MRI scanner. Magnetic strength 1.5 Tesla.
A. Sagittal T1-weighted, TR- 510, TE- 10, slice thickness- 3.0 mm.
B. Sagittal T2-weighted, TR- 3050, TE- 90, slice thickness- 3.0 mm





| | |
|---|---|
| **ETIOLOGY** | Sustained negative energy state leading to a severe loss of fat stores from the body |
| **INCIDENCE** | Variable |
| **GENDER RATIO** | Male predominance |
| **AGE PREDILECTIONS** | Bimodal age distribution, the majority of cases seen in young adults and then people in their sixth decade and older. |
| **RISK FACTORS** | Anorexia nervosa, AIDS, chronic illness like chronic heart failure, cancer-induced cachexia |
| **TREATMENT** | Nutritional intervention and treatment of underlying disorders |
| **PROGNOSIS** | Reversible |
| **FINDINGS ON IMAGING** | • Often seen in the spine and extremity MRI with standard T1 weighted images appearing as fat-suppressed images while fluid sensitive inversion recovery sequences show poor suppression of fat signal with resultant high signal in soft tissue and bone marrow giving an erroneous impression of generalized marrow infiltrative disorder.<br>• Generally, paucity of subcutaneous and visceral fat on imaging. |

**Table 1:** Summary table of Flip Flop Phenomenon - magnetic resonance imaging pitfall.

| | CT | MRI |
|---|---|---|
| **Serous Atrophy of Bone Marrow** | • Osteopenia and coexistent stress fractures.<br>• Paucity of subcutaneous and visceral fat. | • Striking diffuse hypointensity of bone marrow on T1W images simulating T1 Fat sat images and heterogenous hyperintensity on T2W images and fluid sensitive STIR simulating infiltrative disease. |
| **Pathological marrow infiltrative disorder like metastases, leukemia, multiple myeloma.** | • CT will show frank aggressive lytic or sclerotic bony lesions. | • MRI-High signal intensity in bone marrow on fluid sensitive sequences and low signal intensity on T1-weighted sequences and appears first in the axial skeleton. |
| **Hematopoietic Hyperplasia** | | • MRI -Patchy T1 hypointensity still hyperintense to adjacent muscle/ intervertebral discs with minimal hyperintensity on fluid sensitive sequences |
| **Myelofibrosis** | • CT will show splenomegaly and sites of extramedullary hematopoiesis commonly in a paravertebral location. | • Significant hypo intensity on both T1 and T2W MRI sequences. |
| **Gaucher Disease** | | • MRI-Hypointensity on both T1W and T2 WI and minimal hyperintensity on STIR, however, significantly high signal intensity on fluid sensitive sequences suggest underlying infection or infarction.<br>• Marrow infiltration initially involves the axial skeleton and then the peripheral skeleton. |

**Table 2:** Differential diagnosis table for Flip Flop Phenomenon - magnetic resonance imaging pitfall.





## ABBREVIATIONS

AIDS = Acquired immune deficiency syndrome
CT = Computed Tomography
MRI = Magnetic resonance imaging
SABM = Serous atrophy of bone marrow
STIR = Short-Tau Inversion Recovery
WI = Weighted Image

## KEYWORDS

Flip-flop; serous atrophy of bone marrow; MRI; malnutrition; spine; anemia; weight loss

***Online access***

This publication is online available at:
www.radiologycases.com/index.php/radiologycases/article/view/4271

***Peer discussion***

Discuss this manuscript in our protected discussion forum at:
www.radiolopolis.com/forums/JRCR

***Interactivity***

This publication is available as an interactive article with scroll, window/level, magnify and more features.
Available online at www.RadiologyCases.com

Published by EduRad

www.EduRad.org