

Bone marrow abnormalities detected by magnetic resonance imaging as initial sign of hematologic malignancies

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Abstract

The increasing use of radiological examination, especially magnetic resonance imaging (MRI), will probably increase the risk of unintended discovery of bone marrow abnormalities in patients where a hematologic disease would not be expected. In this paper we present four patients with different hematologic malignancies of non-plasma cell types. In all patients the MRI bone marrow abnormalities represent an initial presentation of the disease. These case reports illustrate the importance of a careful diagnostic follow-up without delay of patients with MRI bone marrow abnormalities, because such abnormalities can represent the first sign of both acute promyelocytic leukemia as well as other variants of acute leukemia.

Introduction

Although bone marrow infiltration by malignant cells shows characteristic patterns on magnetic resonance imaging (MRI),¹ to our knowledge, there are no previous reports of abnormal MRI findings in bone marrow presenting as the first sign of different leukemias. In this case report, we describe four different cases of hematologic malignancies in which abnormal MRI findings preceded the diagnosis of leukemia. Abnormal MRI findings as the first sign of a hematologic malignancy is uncommon, except in multiple myeloma.² The increasing use of MRI is likely to result in an increased detection rate of incidental abnormal MRI findings, in turn leading to an increased rate of diagnosis of otherwise asymptomatic hematologic malignancies.

Case Reports

Case #1

A 63-year-old woman was admitted to hospital with acute pain in her right knee. Her past medical history included meniscal surgery in the same knee and left hip replacement due to osteoarthritis. She was otherwise healthy. An MRI examination of the right knee showed degenerative osteoarthritis, rupture of the medial meniscal tear, and a ruptured Baker's cyst. Of note, the MRI scan also revealed bone marrow abnormalities in the distal femur and proximal tibia metaphysis, consistent with primary bone marrow disease (Figure 1). Peripheral blood cell counts were within normal range, and immunoglobulin levels were normal with no monoclonal bands. Whole skeletal X-ray examination showed no lytic lesions. Taken together, it was concluded that the bone marrow changes seen on MRI were consistent with normal age-related changes without any signs of bone marrow disease.

Two and a half years later, the patient presented with 5 kg of weight loss, restless legs and general malaise. Clinical examination revealed normal vital signs, with absence of lymphadenopathy. Peripheral blood cell counts showed a normocytic/normochromic anemia with a hemoglobin (Hb) level of 8.1 g/dL, a slightly decreased platelet count of $138 \times 10^9/L$, and an increased peripheral white blood cell count (WBC) of $80.1 \times 10^9/L$. Microscopy findings from a peripheral blood smear examination were consistent with chronic myeloid leukemia. Bone marrow karyotyping showed loss of chromosome 7 in some metaphases as the only abnormality, and Philadelphia chromosome or fusion gene were not detected by fluorescence *in situ* hybridization (FISH) or polymerase chain reaction (PCR), respectively. The diagnostic conclusion was atypical chronic myeloid leukemia (aCML).

The patient was initially treated with hydroxyurea, which was subsequently followed by treatment with pegylated interferon. However, disease control was not achieved, with a decrease in normal peripheral blood cell counts. The patient therefore underwent allogeneic stem cell transplantation (allo-SCT) with a sibling donor. The only main complication after engraftment was Grade 1 graft-versus-host disease (GVHD). The patient relapsed 6 months post-transplant. A new donor lymphocyte infusion (DLI) had no effect on her leukemia and she died shortly thereafter.

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Case #2

A previously healthy 21-year-old man presented with a 6-month history of pain in the left buttock, as well as deep in the upper left thigh, and intermittent episodes of night sweats. MRI examination showed moderate intervertebral disc degeneration at levels L2/L3 and L4/L5. In addition, signal abnormalities suggesting bone marrow edema in the pelvis were detected posteriorly in the left iliac crest and spreading forward in the iliac bone along the sacroiliac (SI) joints (Figure 2). The presence of a slightly increased amount of fluid in the adjacent SI joints and mild edema in the sacrum was also noted. The iliac bone marrow changes extended laterally and were not considered to be related to the SI joints. Soft tissue edema was also found in the medial gluteal muscle, adjacent to the iliac crest. The initial diagnosis was bone marrow inflammation or infiltration.

Peripheral blood cell counts revealed mild anemia with a Hb level of 11.2 g/dL, but was otherwise unremarkable. A computerized tomography (CT) scan of the thorax, abdomen, and pelvis showed a slightly enlarged spleen, but no lymphadenopathy. A biopsy from the posterior superior iliac crest showed 20-30% of immature blasts,

consistent with acute leukemia, and a sternal bone marrow smear examination demonstrated >80% of immature blasts and promyelocytes. Immunophenotyping was consistent with acute promyelocytic leukemia (APL), which was confirmed by the presence of the t(15;17) *PML-RARA* fusion gene. There was no evidence of coagulopathy.

The patient was treated with chemotherapy combined with all-*trans* retinoic acid (ATRA). Complete hematologic remission was achieved, with no signs of relapse 2 years post-treatment.

Case #3

A previously healthy 20-year-old man presented with several episodes of pain in his right hip. MRI examination demonstrated abnormal signals in the bone marrow in large areas of the right pelvis, indicating increased water content and a decreased proportion of fat. These changes could not be explained simply by local bone marrow hyperplasia (Figure 3), thus raising strong suspicion for a hematologic malignancy. Similar abnormalities were also detected in the spine, whereas weaker signal abnormalities were observed in the sacrum and iliac bone on the left side. At that point, the patient was asymptomatic and had normal peripheral blood cell counts.

A bone marrow biopsy from the left posterior iliac crest showed 25% of lymphoblasts, consistent with acute lymphoblastic leukemia. Leukemia blast karyotyping showed 46,XY,add(21)(q22)[6]/46,XY[14].ish.amp(21), and the immunophenotype was CD10⁺CD11b⁻CD19⁺CD20⁻CD22⁺CD33⁻CD34⁺CD38⁺CD45^{dim}CD56⁺CD117⁻. Immature lymphoblasts were also detected in bone marrow aspirates from the right side of the pelvis.

A total body CT scan showed well-defined focal changes in both kidneys, and 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET) revealed an FDG-positive lesion in the dorsal aspect of the lower left renal capsule. A slight increase in FDG uptake was also seen throughout the skeleton. Biopsy findings of the lesion in the left kidney were compatible with infiltrative B-acute lymphoblastic leukemia.

The patient was treated with chemotherapy, according to the NOPHO ALL-2008 protocol,³ without allogeneic stem cell transplantation. No signs of relapse were noted at two and a half years post-diagnosis.

Case #4

A 69-year-old woman, with a history of hypothyroidism but otherwise healthy, pre-

sented with rupture of the left semitendinosus muscle that resulted from an assault. Due to persistent pain, she underwent MRI scanning of the left thigh, which showed a healing muscle rupture. However, pronounced patchy signal changes in the bone marrow of the femur and pelvic bone were

also detected, as well as enlarged lymph nodes in both groins (Figure 4).

Serum immunoglobulin levels, serum protein electrophoresis, peripheral blood cell counts, and peripheral blood smear microscopy were all normal. CT-guided biopsy of the abnormal areas found on MRI

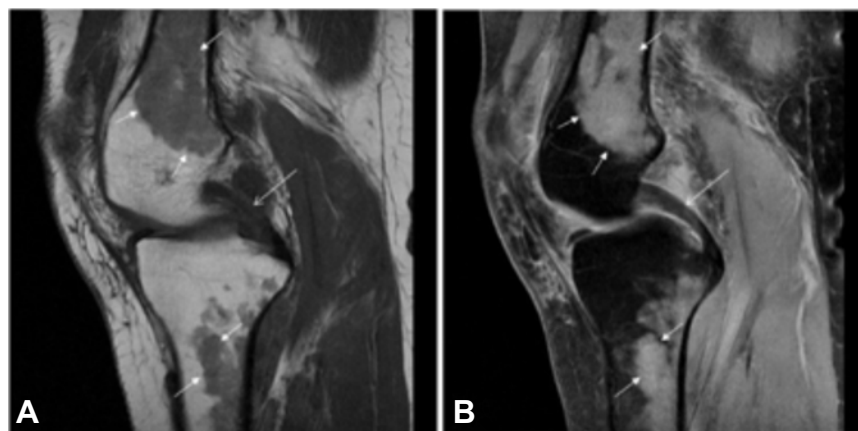


Figure 1. Sagittal T1-weighted (A) and fat suppressed proton-weighted (B) MR images at the level of the posterior cruciate ligament (open arrow) with marked bone marrow signal changes in the distal femur and proximal tibia metaphysis (closed arrows).

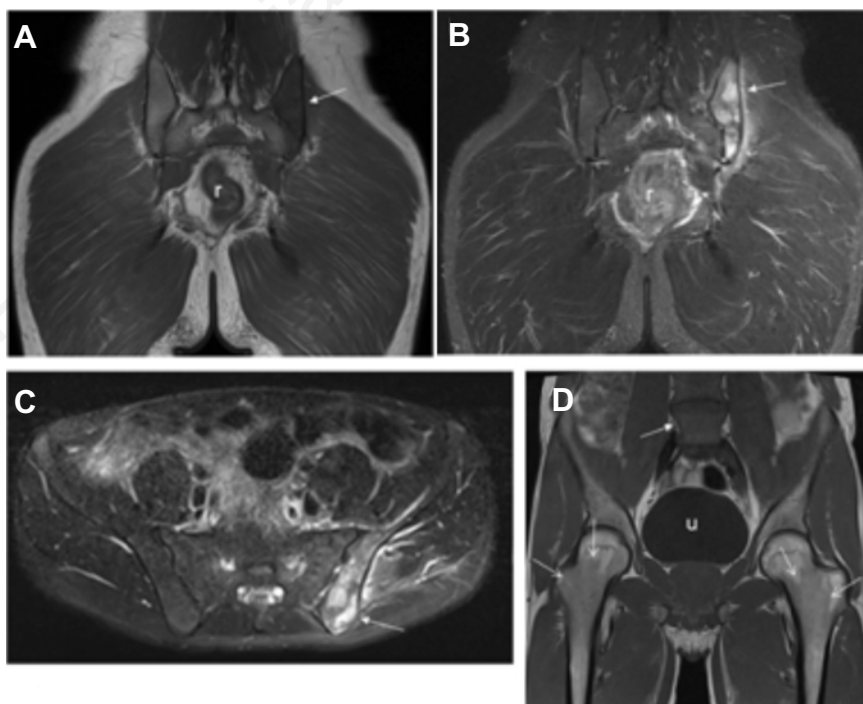


Figure 2. Coronal T1-weighted (A) and fat suppressed T2-weighted (B) MR images at the level of the rectum (r) and axial fat suppressed T2-weighted (C) with signal changes in the posterior iliac crest (closed arrows) indicating bone marrow infiltration. Coronal T1-weighted (D) MR image more anterior through urinary bladder (u) showing unspecific bone marrow changes also in the lower lumbar spine vertebral corpus (closed arrows). The metaphysis and diaphysis of both proximal femurs show more discrete, symmetrical changes, and the bone marrow signal on T1-weighted images is still higher than the signal from muscle tissue probably representing physiological hematopoietic red bone marrow (open arrows).

in the right iliac crest revealed findings consistent with acute lymphoblastic leukemia of B-cell origin (B-ALL). Immunophenotyping of the bone marrow was consistent with B-ALL-related expansion of immature cells (CD10⁺⁺ CD19⁺CD20^{weak} CD22⁺CD38⁺CD58⁺CD34⁺CD45^{weak}).

The patient was treated with chemotherapy plus rituximab. Complete hematologic remission was achieved, with no sign of disease relapse one and a half year post-treatment.

Discussion

This report describes four different cases of hematologic malignancies, in which the malignancy was not suspected based on the absence of symptoms and clinical signs and normal peripheral blood cell counts. However, incidental MRI finding in the bone marrow as part of the initial presentation and diagnostic workup guided to the leukemia diagnosis. With its increasing availability, MRI has become a preferred diagnostic imaging modality for an increasing number of diseases,⁴ which is likely to result in an increased detection rate of incidental findings showing bone marrow abnormalities.⁴ At present, the true incidence of hematologic malignancies in patients with bone marrow abnormalities found as incidental findings on MRI is unknown.^{5,6}

Suspected metastatic disease in the skeletal system is an indication for radiological examination,⁷ whereas plasma cell diseases (including multiple myeloma) are the only hematologic malignancies where radiological bone examination is considered as standard for diagnostic workup.⁸ The four cases presented in this report illustrate that radiological abnormalities can also be part of the initial presentation for non-plasma cell hematologic malignancies.

In Cases #2-4, a diagnosis of acute leukemia was made early following MRI. By contrast, Case #1 was the only case where the diagnosis of a hematologic malignancy was made at a relatively late stage following MRI. Thus, Case #1 suggests that MRI abnormalities can present as an early sign not only for aggressive hematologic malignancies (*i.e.*, acute myeloid and acute lymphoblastic leukemia), but also for chronic myeloproliferative diseases. Cases #3 and #4 together highlight the need for biopsies from affected sites to establish an early correct diagnosis.

In Case #1, abnormal MRI findings were detected 30 months before the diagnosis of a hematologic malignancy was made. Even though definitive evidence for a direct

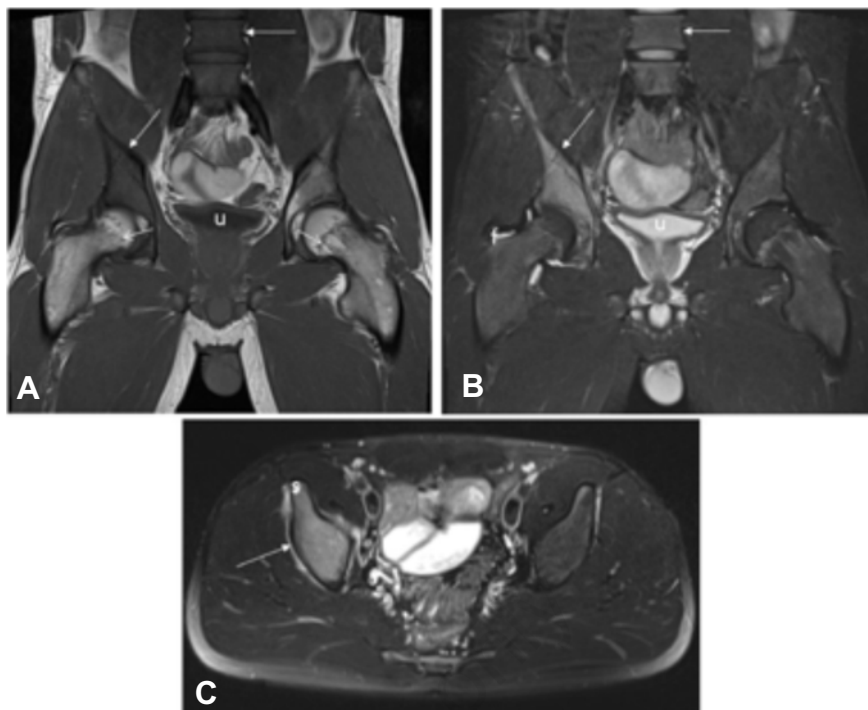


Figure 3. Coronal T1-weighted (A) and fat suppressed T2-weighted (B) MR images through urinary bladder (u) and axial fat suppressed T2-weighted (C) MR images at level of anterior inferior iliac spine (s) with asymmetrical signal changes in the right hemipelvis and lumbar spine (closed arrows) indicating bone marrow infiltration. Small amounts of fluid (f) in right hip joint. Discrete, symmetrical bone marrow changes in the proximal metaphysis of both femurs (open arrows) could be due to physiological hematopoietic red bone marrow.

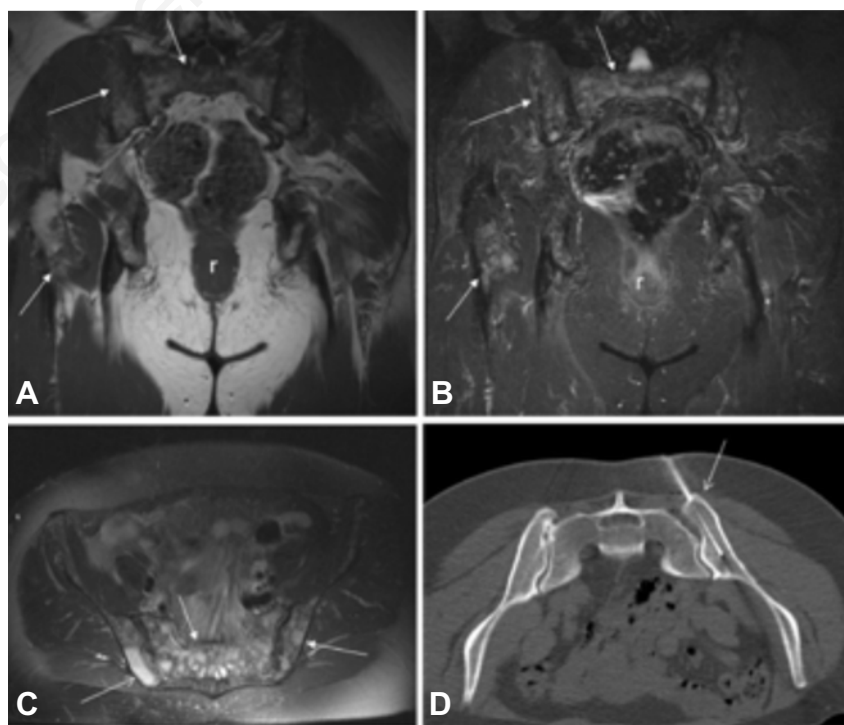


Figure 4. Coronal T1-weighted (A) and fat suppressed T2-weighted (B) MR images through rectum (r) and axial fat suppressed T2-weighted (C) MR images through iliosacral joint (s) with symmetrical, patchy bone marrow signal changes in the sacrum, pelvis and proximal femur (closed arrows). Axial CT image (D) of CT-guided bone biopsy taken from a larger lesion in the right posterior iliac crest (open arrow), patient prone.

association between the abnormal MRI findings and the subsequent diagnosis of malignancy was lacking, the slow progression of such disorders, compared with acute leukemias, and the previously described patchy disease distribution of such less aggressive myeloid malignancies in the of the lower limb strongly suggest that this association is plausible.⁹

Malignancies of both hematopoietic and lymphoid origin were diagnosed in the cases presented here, indicating that these hematologic disorders could both present with pathological MRI findings.^{5,10-12} Current guidelines emphasize the need for rapid diagnostic follow-up in patients with proven or suspected acute leukemias,¹³ and the risk for delayed diagnosis of an aggressive malignancy has to be considered when managing patients with bone marrow abnormalities incidentally found on MRI. Prompt diagnosis is important in patients with APL to avoid early death due to coagulopathy,^{14,15} as well as in patients with non-APL variants of AML and few circulating blasts for long-term leukemia-free survival after treatment.¹⁶

Conclusions

In conclusion, abnormal MRI findings in bone marrow can be part of the initial presentation of hematologic malignancies, as well as the first observation suggesting that further bone marrow examinations are indicated. Physicians should be aware of this possibility, so that further focused and prompt diagnostic follow-up can be instigated. This is of particular importance if acute leukemia is suspected to avoid delayed initiation of treatment.

References

1. Mouloupoulos LA, Dimopoulos MA. Magnetic resonance imaging of the bone marrow in hematologic malignancies. *Blood* 1997;90:2127-47.
2. Takagi S. Magnetic resonance imaging of bone marrow in hematologic malignancies. *Int J Hematol* 1997;66:413-22.
3. Toft N, Birgens H, Abrahamsson J, et al. Risk group assignment differs for children and adults 1-45 yr with acute lymphoblastic leukemia treated by the NOPHO ALL-2008 protocol. *Eur J Haematol* 2013;90:404-12.
4. Orme NM, Fletcher JG, Siddiki HA, et al. Incidental findings in imaging research: Evaluating incidence, benefit, and burden. *Arch Intern Med* 2010;170:1525-32.
5. Silva JR Jr, Hayashi D, Yonenaga T, et al. MRI of bone marrow abnormalities in hematological malignancies. *Diagn Interv Radiol* 2013;19:393-9.
6. Navarro SM, Matcuk GR, Patel DB, et al. Musculoskeletal imaging findings of hematologic malignancies. *Radiographics* 2017;37:881-900.
7. Karchevsky M, Babb JS, Schweitzer ME. Can diffusion-weighted imaging be used to differentiate benign from pathologic fractures? A meta-analysis. *Skeletal Radiol* 2008;37:791-5.
8. Dutoit JC, Verstraete KL. MRI in multiple myeloma: a pictorial review of diagnostic and post-treatment findings. *Insights Imaging* 2016;7:553-69.
9. Keraliya AR, Krajewski KM, Jagannathan JP, et al. Multimodal imaging of osseous involvement in haematological malignancies. *Br J Radiol* 2016;89:20150980.
10. Shih TT, Hou HA, Liu CY, et al. Bone marrow angiogenesis magnetic resonance imaging in patients with acute myeloid leukemia: peak enhancement ratio is an independent predictor for overall survival. *Blood* 2009;113:3161-7.
11. Rahmouni A, Montazel JL, Divine M, et al. Bone marrow with diffuse tumor infiltration in patients with lymphoproliferative diseases: dynamic gadolinium-enhanced MR imaging. *Radiology* 2003;229:710-7.
12. Tsunoda S, Takagi S, Tanaka O, Miura Y. Clinical and prognostic significance of femoral marrow magnetic resonance imaging in patients with malignant lymphoma. *Blood* 1997;89:286-90.
13. Döhner H, Weisdorf DJ, Bloomfield CD. Acute myeloid leukemia. *N Engl J Med* 2015;373:1136-52.
14. Sanz MA, Grimwade D, Tallman MS, et al. Management of acute promyelocytic leukemia: recommendations from an expert panel on behalf of the European LeukemiaNet. *Blood* 2009;113:1875-91.
15. Breen KA, Grimwade D, Hunt BJ. The pathogenesis and management of the coagulopathy of acute promyelocytic leukaemia. *Br J Haematol* 2012;156:24-36.
16. Sekeres MA, Elson P, Kalaycio ME, et al. Time from diagnosis to treatment initiation predicts survival in younger, but not older, acute myeloid leukemia patients. *Blood* 2009;113:28-