Annals of Diagnostic Pathology 40 (2019) 7–12

Contents lists available at ScienceDirect

Annals of Diagnostic Pathology

journal homepage: www.elsevier.com/locate/anndiagpath

Radiological-Pathological Correlation

Hematolymphoid neoplasms are common in bone marrow biopsies performed for non-specific, diffuse marrow signal alterations on magnetic resonance imaging

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ARTICLE INFO

Keywords:
Hematolymphoid neoplasm
Magnetic resonance imaging
MRI
T1 signal alteration

ABSTRACT

Aims: MRI is an imaging modality used for a wide range of clinical indications. Occasionally, non-specific, diffuse T1 marrow signal alterations are identified, which may prompt a bone marrow biopsy (BM). However, there is little data on the clinicopathologic significance of this signal alteration. This study evaluated the frequency and nature of pathologic findings in BM performed to evaluate diffuse MRI T1 marrow signal alterations.
Methods: Records from January 2003 to May 2015 were searched for BM performed to evaluate abnormal MRIs. 179 cases were identified. Patients with nodular/destructive bone lesions on MRI or other imaging studies, or a previous diagnosed metastatic tumor or hematologic malignancy were excluded, resulting in 45 cases.
Results: The patients included 22 males and 23 females with a median age of 56 years. The location of the MRI T1 marrow signal alterations included spine, pelvis, knee, skull, femur, and arm. 19/45 patients had neoplasms identified in the BM. The remaining 26 patients had benign BM findings. There was a significant difference in hemoglobin values in patients with neoplastic versus benign BM findings ($p = 0.037$, unpaired Student's *t*-test).
Conclusions: Diffuse T1 marrow signal alterations on MRI should warrant a BM evaluation, as 42% of cases showed an underlying hematolymphoid neoplasm or metastatic tumor, even when patients with a known history of malignancy were excluded. When faced with a BM from a patient with a non-specific, diffuse MRI signal alteration, a pathologist should have a high index of suspicion for a malignant neoplasm, most often of hematopoietic/lymphoid type.

1. Introduction

Magnetic resonance imaging (MRI) is a diagnostic imaging modality used for a wide range of clinical indications due to its ability to provide soft tissue contrast that is substantially better than other imaging modalities [1-7]. MRI also allows highly detailed assessment of bone marrow signal characteristics in imaged osseous structures [1-6,9]. Therefore, MRI has become increasingly preferred over other imaging modalities for assessing bone marrow-based disorders [1-6]. MRI has a high sensitivity for the identification of tumors and inflammatory processes in bone marrow, and studies have also demonstrated its utility in the evaluation of hematologic malignancies, particularly in the staging evaluation of patients with plasma cell neoplasms [1-8].

During normal development, bone marrow undergoes a physiologic transition from hematopoietic (red) marrow to fatty (yellow) marrow in a predictable fashion, beginning in childhood at the periphery of the appendicular skeleton and progressing toward the central axial skeleton [1,3,5]. The adult pattern of hematopoietic marrow distribution, largely concentrated in the axial skeleton, is usually achieved by the age of 25 years [1-4]. Of the routine MRI sequences available, T1-weighted imaging without fat suppression is one of the most helpful in elucidating alterations in the normal marrow distribution [3,4,10]. Normal fatty marrow appears hyperintense relative to skeletal muscle and isointense to subcutaneous fat in T1-weighted images, while malignant or benign processes that alter this normal distribution will generally appear T1 hypointense compared to normal marrow signal [3-5,10]. There are a variety of etiologies that may lead to T1 signal alterations on MRI, including reconversion from fatty to hematopoietic marrow (bone marrow hyperplasia), fractures, chemotherapy, osteonecrosis, infection, osteoarthritis or inflammatory arthritides, myelofibrosis, aplastic anemia, hematolymphoid neoplasms, and other primary or metastatic tumors [1,3,4,11]. These disturbances in marrow cellularity

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https://doi.org/10.1016/j.anndiagpath.2019.02.002

may result in focal, multifocal or diffuse T1 signal abnormalities [1,3,4,11].

However, the increasing use of MRI over the past two decades has also led to an increase in incidental findings in the bone marrow, which may or may not be associated with clinically significant disease [12-19]. When incidental marrow signal alterations are identified on MRI they may prompt a bone marrow biopsy and other laboratory investigations to exclude the possibility of an underlying malignancy. There have only been a few studies that have evaluated the clinicopathologic significance of diffuse, non-specific signal alterations identified on MRI, most of which include only a limited number of patients with corresponding bone marrow biopsy evaluations [15,18-20]. Therefore, it is still unclear if bone marrow evaluations are required in all patients with incidental diffuse, non-specific MRI marrow signal alterations. In an attempt to further answer this question, we evaluated the frequency and nature of pathologic findings in bone marrow biopsies performed on 45 patients to evaluate for non-specific, diffuse T1 marrow signal alterations identified on MRI.

2. Materials and methods

An electronic search of the pathology and radiology records of the institution was performed using the TIES clinical text search engine after approval by the Institutional Review Board. The electronic search included all patients with bone marrow biopsies performed as a result of abnormal MRI studies obtained between January 2003 and May 2015. One hundred seventy-nine cases were initially identified. Only patients with MRI studies showing a generalized T1 marrow signal alteration in the imaged osseous structures were included in the study. Therefore, any patients that had single or multiple nodular or destructive bone lesions identified on MRI or other imaging studies were excluded. In addition, any patients with a known history of metastatic tumor or other previously diagnosed hematolymphoid neoplasm were excluded from the study. One additional patient was excluded as the MRI study was performed after the bone marrow biopsy had been obtained, resulting in 45 cases for review. The bone marrow aspirate smears and biopsies or particle preparations/clot sections, as well as all ancillary studies including immunohistochemistry, flow cytometry, classical cytogenetics and molecular studies, were reviewed to confirm the diagnosis for each case. In addition, all available clinical and laboratory data from the time of diagnosis and at follow-up was reviewed.

3. Results

3.1. Clinical features

The patients included 22 males and 23 females with a median age of 56 years (range 3–84 years) (Table 1). The anatomic location of the MRI studies included spine (n = 31), pelvis (n = 7), knee (n = 4), brain/skull (n = 2), femur (n = 1), and arm (n = 1). The indications for MRI included pain at the anatomic site of the MRI study (i.e. pelvic pain as an indication for pelvic MRI) in 14/45 patients, pain at the anatomic site associated with additional symptoms (i.e. lumbar spine MRI for back pain and leg paresthesias) in 25/45 patients, and other indications (i.e. MRI performed for stroke protocol) in 6/45 patients. The bone marrow MRI signal abnormalities in the cases that had other indications were thought to be incidental.

3.2. Pathologic review of bone marrow specimens

Nineteen patients (42%) had neoplastic findings in the bone marrow biopsies including 15 with hematolymphoid neoplasms (Table 2). The hematolymphoid neoplasms included 4 B-cell non-Hodgkin lymphomas (1 follicular lymphoma, 1 diffuse large B-cell lymphoma, 1 chronic lymphocytic leukemia/small lymphocytic lymphoma, and 1 lymphoplasmacytic lymphoma), 3 B-lymphoblastic leukemia/lymphomas, 2 plasma cell myelomas, 2 monoclonal gammopathy of undetermined significance, 2 myeloproliferative neoplasms (1 chronic myeloid leukemia, *BCR-ABL1*-positive and 1 primary myelofibrosis), and 2 myelodysplastic syndromes (1 myelodysplastic syndrome with unilineage dysplasia and 1 myelodysplastic syndrome with ring sideroblasts) (Figs. 1 and 2). The remaining 4 patients were found to have metastatic tumors including 3 metastatic carcinomas (1 breast and 2 unknown primaries) and 1 metastatic neuroblastoma.

Table 1
Clinical features of 45 patients with diffuse, non-specific MRI marrow signal alterations.

Median age in years (range)	56 (3–84)
Gender	22 M/23 F
MRI site[a]	
Spine	31 (67%)
Pelvis	7 (15%)
Knee	4 (9%)
Brain/skull	2 (4%)
Femur	1 (2%)
Arm	1 (2%)
Indications for MRI	
Pain at anatomic site of MRI study	14 (31%)
Pain at anatomic site of MRI study and associated additional symptoms	25 (56%)
Other indications	6 (13%)

Abbreviations: MRI, magnetic resonance imaging; M, male; F, female.
[a] One patient had both pelvis and femur MRIs.

The remaining 27 patients had benign bone marrow findings including 8 patients whose bone marrow contained reactive lymphoid aggregates, 7 patients who had hypocellular or hypercellular bone marrows with non-specific changes, 4 patients with erythroid hyperplasia, 1 patient with granulomatous inflammation in the bone marrow, and 7 patients with no significant bone marrow abnormalities (Table 2, Figs. 3 and 4). Four of the 8 patients with reactive lymphoid aggregates in the bone marrow had underlying autoimmune disorders including systemic lupus erythematosus, rheumatoid arthritis, undifferentiated connective tissue disease, and pernicious anemia. Two additional patients had underlying infections including hepatitis B and *Staphylococcus aureus* sepsis. The remaining 2 patients with reactive lymphoid aggregates in the bone marrow included one patient with a prior history of anal and lung carcinoma status post therapy, and one patient with a history of chronic knee pain and mild macrocytic anemia.

Seven of 27 patients had bone marrow biopsies with non-specific reactive changes including mild dyspoiesis in myeloid, erythroid or megakaryocytic lineages or a mild left shift in myeloid or erythroid maturation. These changes were not felt to be sufficient for the diagnosis of an underlying myeloid neoplasm, and cytogenetic and/or molecular studies performed on the bone marrows also did not show evidence of a clonal population. Three of 7 biopsies were hypocellular, 2 of 7 were hypercellular, and 2 had inadequate bone marrow biopsies to assess marrow cellularity. Four of 7 patients had a history of infection including HIV, hepatitis C, infectious mononucleosis, and group B streptococcus, one patient had a history of systemic lupus erythematosus, one patient was found to have a low level serum monoclonal gammopathy without evidence of clonal plasma cells in the bone marrow, and one patient had no significant past medical history and was subsequently diagnosed with lumbar radiculopathy. Three of the 7 patients had normal complete blood counts (CBC), while 2 had a mild microcytic anemia, one had mild neutropenia, and one had pancytopenia.

Four of 27 patients had bone marrow biopsies showing erythroid hyperplasia, and included 2 patients with a history of smoking, but minimal associated erythrocytosis, 1 patient with iron deficiency anemia, and 1 patient with a history of hereditary spherocytosis. One of the 27 patients had several small, non-caseating granulomas in the bone

Table 2
Diagnoses, pattern of T1 signal alterations, and hematologic parameters in 45 patients with diffuse, non-specific MRI marrow signal alterations.

Bone marrow diagnosis	Pattern of MRI T1 Marrow signal alterations[a]		Hematologic parameters[c]		
	Confluent (18 patients)	Heterogeneous (28 patients)[b]	Median WBC (range)	Median Hb (range)	Median Plt (range)
Neoplastic	10	9	5.9 (3–25.3)	11.4[d] (8.0-14.8)	203 (61–347)
Myeloproliferative neoplasm	1	1	16.8 (8.3–25.3)	12.1 (9.3–14.8)	179 (155–203)
Myelodysplastic syndrome	1	1	4.9 (3.1–6.6)	12.3 (12.2–12.3)	178 (93–262)
B-cell non-Hodgkin lymphoma	2	2	3.8 (3.3–5.4)	10.7 (8.0–12.1)	135 (104–186)
Plasma cell myeloma	0	2	4.7 (3.5–5.9)	10.7 (10.0–11.3)	284 (252–316)
Monoclonal gammopathy of undetermined significance	0	2	6.9 (6.4–7.3)	12.1 (11.6–12.6)	288 (240–335)
B-lymphoblastic leukemia/lymphoma	3	0	5.2 (3.0–10.7)	10.7 (10.0–11.7)	333 (138–347)
Metastatic carcinoma	2	1	8.1 (4.9–11.3)	11.4 (10.5–13.2)	200 (61–224)
Metastatic neuroblastoma	1	0	11.6	10.2	316
Benign	8	19	6.8 (0.7–10.5)	13.2[d] (8.2-16.2)	227 (119–556)
Reactive lymphoid aggregates	2	6	6.9 (2.7–10.5)	13.5 (8.4–14.7)	227 (191–444)
Granulomatous inflammation	0	1	6.4	9.3	243
Erythroid hyperplasia	1	3	6.3 (4.4–9.0)	13.3 (10.0–14.9)	212 (180–240)
Non-specific reactive changes[e]	4	3	6.6 (0.7-8.3)	10.4 (8.2–14.4)	241 (137–556)
No significant abnormalities	1	6	7.4 (5.9–9.1)	14.5 (13.2–16.2)	232 (119–349)

Abbreviations: MRI, magnetic resonance imaging; WBC, white blood cell count ($\times 10^9$/L); Hb, hemoglobin (g/dL); Plt, platelets ($\times 10^9$/L).

[a] There was no statistically significant difference in the pattern of MRI T1 signal alterations between neoplastic and benign bone marrow biopsies (p = 0.1, two-tailed Fisher's exact test).

[b] Includes one patient with two benign bone marrow biopsies.

[c] Hematologic parameters were available for 42/45 patients.

[d] Hb values were significantly different between patients with neoplastic versus benign bone marrow findings (p = 0.037, unpaired Student's *t*-test).

[e] Cases with non-specific reactive changes had mild dyspoiesis or a mild left shift in myeloid or erythroid maturation insufficient for the diagnosis of an underlying myeloid neoplasm.

marrow biopsy, which were negative for acid-fast bacilli and fungal stains. Although this patient was subsequently found to have iron deficiency anemia, no infectious or autoimmune etiology to explain the granulomatous inflammation was identified.

The remaining 7 patients had bone marrow biopsies that were normocellular for age and showed no significant abnormalities. Three of these 7 patients had no significant past medical history other than pain at the MRI site, and had normal CBCs. One of 7 patients had a history of systemic lupus erythematosus, one had a history of smoking with mild erythrocytosis, one had a low level serum monoclonal gammopathy with a normal CBC and no evidence of clonal plasma cells in the bone marrow, and one had a history of non-metastatic prostatic adenocarcinoma and recently developed mild thrombocytopenia.

When reviewing available CBC data from 42 of 45 patients at the time of bone marrow biopsy, 31/42 patients (74%) had abnormalities. All 19/19 patients with neoplastic bone marrow findings had CBC abnormalities, whereas 12/23 (52%) patients with benign bone marrow findings had CBC abnormalities. There was a significant difference in

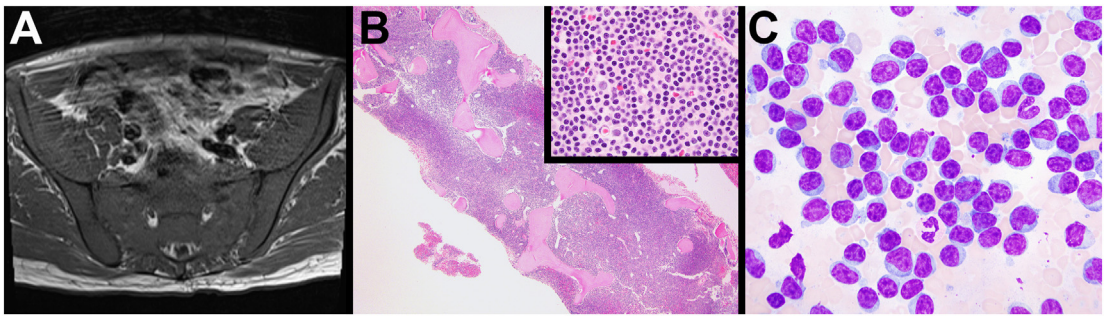

Fig. 1. Pelvic MRI and bone marrow biopsy of a 56-year-old male diagnosed with chronic lymphocytic leukemia/small lymphocytic lymphoma. Axial T1-weighted MRI sequence showed confluent low T1 marrow signal intensity in the imaged pelvis and sacrum (A). The bone marrow biopsy (B) and aspirate (C) showed extensive involvement by chronic lymphocytic leukemia/small lymphocytic lymphoma (B, H&E stain, C, Wright stain; B, magnification ×40 and 1000 (inset), C, magnification ×1000).

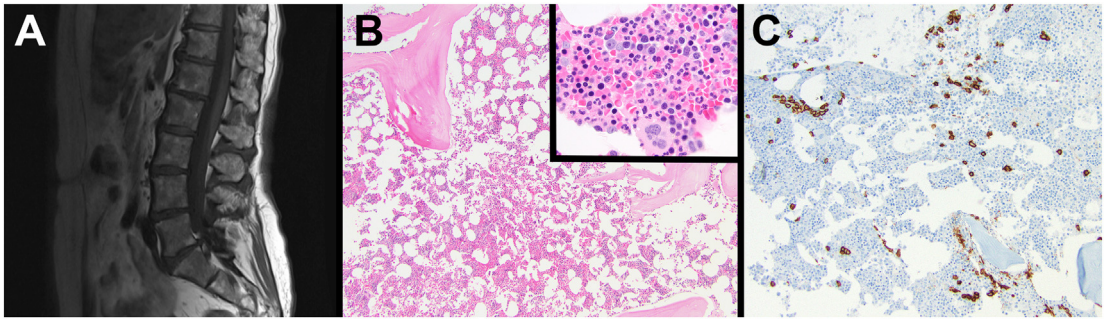

Fig. 2. Lumbar spine MRI and bone marrow biopsy of a 71-year-old female diagnosed with monoclonal gammopathy of undetermined significance. Sagittal T1-weighted MRI sequence showed diffuse and heterogeneous low T1 marrow signal intensity in the lumbar spine (A). The patient was found to have an IgM lambda serum monoclonal protein (0.3 g/dL) and the bone marrow biopsy (B) showed a normocellular bone marrow with < 10% CD138-positive plasma cells (C) (B, H&E stain, C, immunohistochemical stain with hematoxylin counter stain; B, magnification ×100 and 1000 (inset), C, magnification ×200).

hemoglobin values in patients with neoplastic versus benign bone marrow findings (median 11.4 g/dL versus 13.2 g/dL, p = 0.037, unpaired Student's *t*-test). There were no significant differences in the white blood cell count or platelet count identified between patients with neoplastic bone marrow findings versus those with benign bone marrow findings (p > 0.05, unpaired Student's *t*-test).

3.3. Correlation of bone marrow pathologic findings with radiologic features

All 45 patients had diffuse low T1 marrow signal alterations relative to normal marrow on MRI. Although 18 cases had confluent hypointense T1 marrow signal in the imaged anatomic sites, 28 cases exhibited more heterogeneity in the hypointense T1 signal (Table 2, Figs. 1–4). There was no statistically significant difference in the pattern of T1 marrow signal alteration between neoplastic and benign bone marrow biopsies (p = 0.14, two-tailed Fisher's exact test). However, all patients diagnosed with plasma cell myeloma or monoclonal gammopathy of undetermined significance had a heterogeneous pattern of MRI T1 signal alteration. Although patients with bone marrow biopsies that contained reactive lymphoid aggregates or showed no significant abnormalities also tended to have a heterogeneous pattern of T1 signal alteration (6/8 bone marrows with lymphoid aggregates and 6/7 bone marrows with no significant abnormalities), this finding was not statistically significant (p > 0.2, two-tailed Fisher's exact test).

4. Discussion

MRI is indicated in a wide variety of clinical situations due to its ability to provide enhanced soft tissue contrast [1-7]. However, the growing use of this imaging modality comes with an increase in the detection of incidental findings, which may or may not be associated with clinically significant disease [12-19]. In the literature it has been estimated that incidental findings of clinical relevance may be detected by MRI in 10–34% of patients, although this does vary based on the anatomic region imaged [12-16]. These incidental findings appear to most commonly involve abdominal organs, the urinary tract, pulmonary system, and skeletal system [12-15].

Only a few studies have evaluated the incidence and clinical significance of incidental abnormal bone marrow signals detected on MRI [18-20]. One study of almost 50,000 MRIs performed during a 5 year period reported that < 1% of studies demonstrated incidental abnormal bone marrow signal [18]. Importantly, malignant diagnoses were found in 6% of the patients with incidental abnormal bone marrow signal in this study, which comprised 25% of all patients who underwent further clinical workup, and included 4 patients with hematologic malignancies and 2 patients with metastatic carcinoma [18]. However, this study is somewhat limited in that it failed to describe the radiologic features of the abnormal MRI marrow signal that defined the study cohort, and that only 22% of the patients in this study received any additional clinical evaluation after the abnormal bone marrow signal was reported [18]. Therefore, the true incidence of clinically significant findings and the overall frequency of incidental diffuse marrow signal alterations on MRI remains uncertain. Unfortunately, the design of our study does not allow for this determination as our initial electronic search only included patients who had subsequent bone marrow biopsies performed, and likely missed patients that were not referred for additional clinical evaluation in our health system.

Similar to our study, Spierings et al retrospectively examined 15 patients with diffuse T1 marrow signal alterations incidentally detected on MRI that had subsequent bone marrow biopsies performed [19]. In this series, 47% of the patients had clinically significant hematologic disorders identified, including 3 patients with myeloid neoplasms, 2 patients with plasma cell neoplasms, 1 patient with classic Hodgkin lymphoma, and 1 patient with hereditary spherocytosis [19]. This is

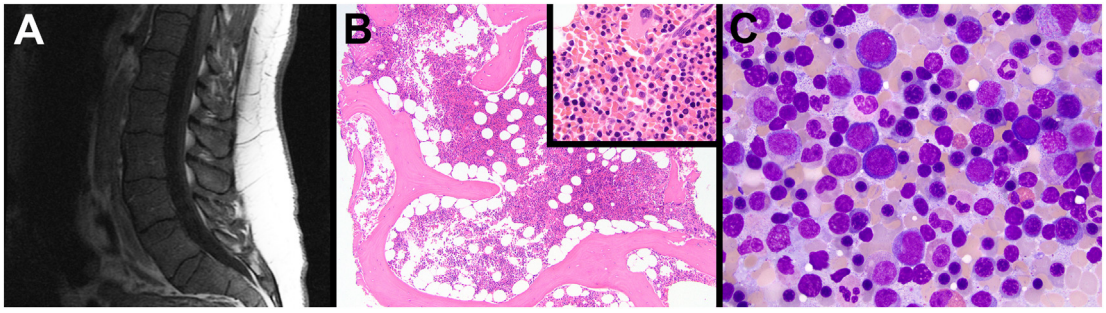

Fig. 3. Lumbar spine MRI and bone marrow biopsy of a 43-year-old male whose bone marrow biopsy showed mild erythroid hyperplasia. Sagittal T1-weighted MRI sequence showed confluent low T1 marrow signal intensity in the lumbar spine (A). The patient had normal CBC parameters and the bone marrow biopsy (B) and aspirate (C) showed a normocellular bone marrow with mild erythroid hyperplasia, but no other findings suggestive of an underlying myeloid neoplasm (B, H&E stain, C, Wright stain; B, magnification ×100 and 1000 (inset), C, magnification ×1000).

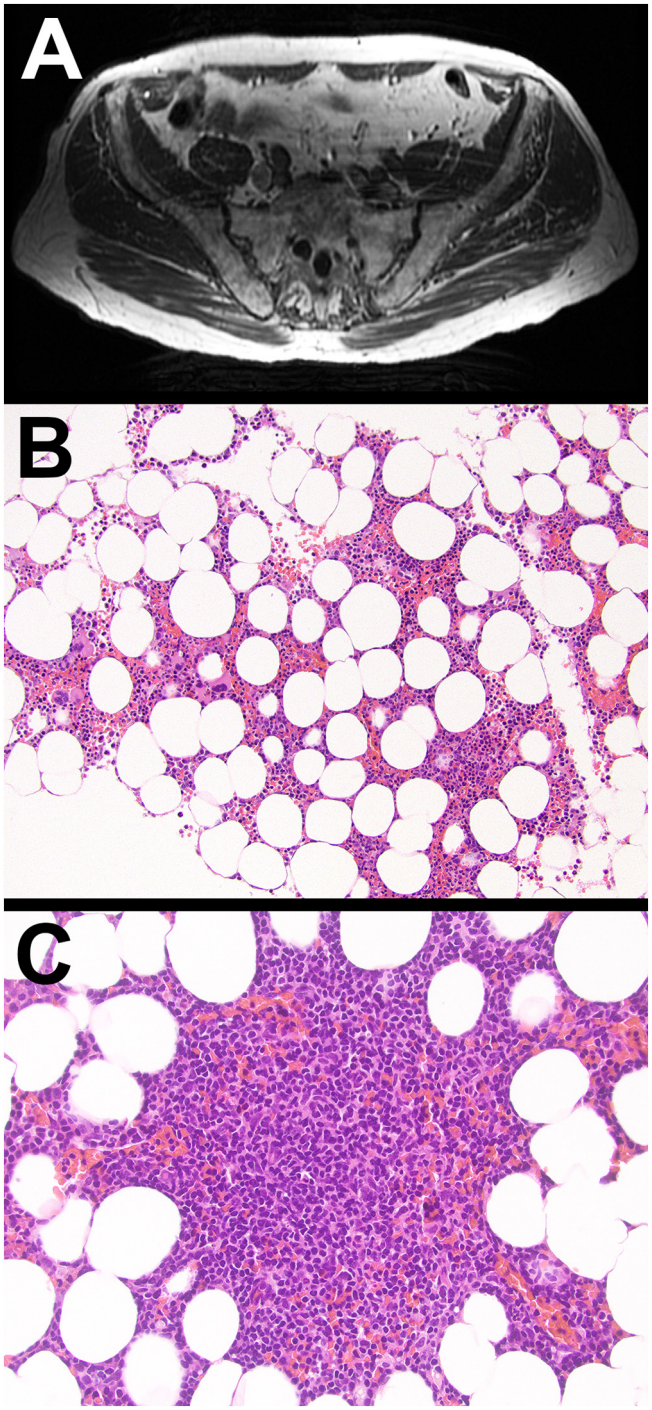

Fig. 4. Pelvic MRI and bone marrow biopsy of a 78-year-old male whose bone marrow biopsy showed non-specific changes and scattered reactive lymphoid aggregates. Axial T1-weighted MRI sequence showed diffuse and heterogeneous low T1 marrow signal intensity in the imaged pelvis and sacrum (A). The patient had a known history of pernicious anemia and was found to have a mild normocytic anemia (hemoglobin 13.6 g/dL). The bone marrow biopsy showed a normocellular bone marrow (B) with occasional reactive lymphoid aggregates (C) (B–C, H&E stain; B, magnification ×200, C, magnification ×400).

comparable to the results of our study, which showed that 42% of patients with diffuse MRI T1 marrow signal abnormalities had neoplastic bone marrow findings, of which 79% of the cases represented hematolymphoid neoplasms. Although our study also found that patients with neoplastic bone marrow findings tended to have a lower hemoglobin value, Spierings et al found no differences in CBC values between patients with hematologic disorders and those with normal bone marrow findings [19].

The findings in our study and that of Spierings et al are somewhat different from those reported by Deutsch et al, who reviewed 10 patients with knee MRIs showing diffuse T1 marrow signal alterations in the distal metaphysis of the femur [20]. Although only 3 patients underwent bone marrow biopsies and 2 underwent open biopsies of the distal femur, these biopsies showed mild to moderate bone marrow hypercellularity with no evidence of a neoplastic process [20]. Five of 9 patients had normal CBCs, while 4 patients had a mild to moderate leukocytosis ranging from 12.0 to 16.0 $\times 10^9$/L, which was felt to be related to cigarette smoking [20]. In contrast, our study and that of Spierings et al found CBC abnormalities in 74–80% of patients with diffuse MRI T1 marrow signal alterations [19]. However, given that both our study and that of Spierings et al only included patients in whom bone marrow biopsies were performed, there may be a selection bias for patients with CBC abnormalities and an increased probability of detecting a hematologic disorder.

MRI allows highly detailed assessment of the bone marrow signal, but, in some cases, it may be difficult to differentiate between benign and malignant processes based on the imaging features, and the differential diagnosis of diffuse T1 marrow signal alterations remains broad [1,3,11,18]. Although diffuse T1 marrow signal alterations may be seen in primary hematologic malignancies such as acute leukemias, myeloproliferative neoplasms, lymphomas, and even plasma cell myeloma, benign processes, in particular reactive bone marrow hyperplasia, can have a similar radiologic appearance [1,3,11]. The diffuse marrow signal alterations identified in our study cohort did vary somewhat from a confluent hypointense T1 signal in 18/45 patients to a more heterogeneous hypointense T1 signal in 28/45 patients. However, there was no significant difference in the pattern of T1 marrow signal alteration between patients with neoplastic bone marrow findings and those with benign findings. Importantly, our study and those of others have not shown distinct radiologic or CBC parameters that can completely aid in differentiating between benign and malignant diagnoses in patients with these diffuse MRI T1 marrow signal alterations [18,19].

In conclusion, a high proportion of patients with incidental, diffuse T1 marrow signal alterations on MRI will be found to have neoplastic bone marrow findings, primarily hematolymphoid neoplasms, but also occasional metastatic tumors. As a result, radiologists, primary care physicians, and pathologists should have a high index of suspicion for malignancy in these cases. Our data, as well as that previously reported by others, would suggest that when these incidental marrow signal abnormalities are detected on MRI, further laboratory investigations and bone marrow evaluations to assess for cancer risk should be pursued [18,19].

Declarations of interest

None.

Acknowledgements

The TIES system is supported by Grant Number R01 CA132672 from the National Cancer Institute (NCI) and Grant Number 2ULRR024153 from the National Center for Advancing Translational Sciences (NCATS).

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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