Added Value of Contrast-Enhanced T1-Weighted and Diffusion-Weighted Sequences for Characterization of Incidental Findings on Whole Body Magnetic Resonance Imaging in Plasma-Cell Disorders

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Abstract

Incidental findings on whole body magnetic resonance imaging (WBMRI) in myeloma may necessitate additional investigations. Incidence, characterization, and significance of incidental findings at WBMRI in 100 patients with plasma-cell disorders were calculated. A total of 348 findings were detected in 97 of 100 patients; 38 of 348 findings were indeterminate, and no additional cancers were detected. Incidental findings are common, but the majority can be characterized at WBMRI and are not significant.

Background: Whole body magnetic resonance imaging (WBMRI) is currently recommended by guidelines for the assessment of myeloma. This will inevitably result in incidental findings. We aimed to assess the frequency of extraskeletal incidental findings and the added value of contrast-enhanced (CE) T1-weighted (T1-W) and diffusion-weighted (DWI) sequences for their characterization in a single WBMRI examination.

Patients and Methods: We performed 1.5 T WBMRI in 100 patients (53 female; median age, 65 years) with plasma-cell disorders from January 2014 to July 2017. T2-weighted sequences were reviewed initially for incidental findings, followed by sequential review of T1-W, CE T1-W, and DWI sequences for lesion characterization. Descriptive statistics were undertaken.

Results: A total of 348 incidental findings were detected in 97 (97%) of 100 patients; only 38 (10.9%) of 348 findings were indeterminate. T1-W sequences increased diagnostic confidence in the characterization of 12 (31.6%) of 38; CE T1-W sequences in the characterization of 16 (50%) of 32; and DWI increased diagnostic confidence in 21 (55.3%) of 38 compared to the T2-weighted sequence alone.

Conclusion: Incidental findings are common, but the majority are of no clinical consequence. No additional cancers were noted in our series. DWI and CE T1-W sequences increased diagnostic confidence in 50% of indeterminate findings and may reduce the need for further investigation.

Keywords: Diffusion magnetic resonance imaging, Magnetic resonance imaging, Multiple myeloma, Whole body imaging

Introduction

The revised International Myeloma Working Group guidelines now state that the presence of more than one focal magnetic resonance imaging (MRI) bone lesion > 5 mm is diagnostic of myeloma.1 The International Myeloma Working Group guidelines also specifically advocate whole body magnetic resonance imaging (WBMRI) in the initial assessment of smoldering myeloma because patients are at increased risk of progression to myeloma. With its

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Keywords: Diffusion magnetic resonance imaging, Magnetic resonance imaging, Multiple myeloma, Whole body imaging
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Excellent tissue contrast and high spatial resolution, WBMRI provides a comprehensive approach to skeletal and extraskeletal assessment. WBMRI will define disease burden through the number and location of skeletal lesions, the pattern of disease, and the presence of extraosseous sites, as well as clinically significant complications such as fractures and cord/cauda equina compression.

Thus clinical practice guidelines are changing. Whole body MRI (WBMRI) is now recommended in the United Kingdom by the National Institute for Health and Care Excellence as the first-line imaging test for suspected and newly diagnosed myeloma.\(^2\) The 2017 British Society of Haematology guidelines also recommend WBMRI as the first-line imaging test in asymptomatic patients with 10% to 60% plasma cells on trephine biopsy or bone marrow aspirate, or an M protein level of 30 g/L.\(^3\)

Incidental findings are inevitable with whole body studies and may require further investigations, adding to patient anxiety. Up to 58% of incidental findings may be indeterminate in nature.\(^4\) We hypothesized that a comprehensive WBMRI protocol including T2-weighted (T2-W), T1-weighted (T1-W), contrast-enhanced (CE) T1-W, and diffusion-weighted (DWI) sequences will improve the characterization of incidental findings and potentially reduce the need for further investigations. We thus aimed to determine (1) the frequency of incidental findings in patients undergoing WBMRI for plasma-cell disorders in our institution, (2) their clinical significance, and (3) the added value of T1-W, CE T1-W, and DWI sequences in the characterization of indeterminate findings.

Patients and Methods

Patients

Institutional review board approval was obtained; the need for informed consent was waived for this retrospective audit of practice. One hundred patients with suspected or proven plasma-cell disorders underwent WBMRI between January 2014 and July 2017. There were 53 female and 47 male patients with a median age of 65 years (range, 38-90 years) who had the following confirmed diagnoses: myeloma = 63, smoldering myeloma = 11, monoclonal gammopathy of unknown significance = 12, plasmacytoma = 6, and other diagnoses = 8 (suspected myeloma = 3, amyloidosis = 3, lymphoma = 1, demyelinating neuropathy = 1).

Imaging and Image Analysis

WBMRI consisting of T2-W, T1-W, DWI (b-value = 50 and 900 s/mm\(^2\)), and CE T1-W sequences from the skull vertex to knees was performed at 1.5 T (Magnetom Aera; Siemens Healthcare, Erlangen, Germany) (Table 1). WBMRI study duration was approximately 45 minutes. Intravenous contrast administration (20 mL gadoterate meglumine) was only possible in 82 (82%) of 100 patients because of renal impairment.

T2-W sequences were reviewed initially for incidental findings, followed by a dedicated review of T1-W, CE T1-W, and DWI sequences including apparent diffusion coefficient maps by a staff radiologist with 7 years of MRI experience. Findings, their site, and likely diagnoses were noted. On the basis of review of T2-W sequences, these findings were also categorized as follows: I, common in asymptomatic subjects/not clinically significant; IIa, benign and potentially clinically significant; IIb, indeterminate and potentially malignant; or III, requiring urgent clinical input.

For indeterminate findings that could not be characterized initially on the T2-W sequence, the likelihood of malignancy was recorded for each additional sequence (T1-W, CE T1-W, and DWI) as follows: I, benign, II, probably benign, III, indeterminate, IV, probably malignant, or V, malignant.

The diagnostic confidence for likely diagnosis was also scored for T1-W, CE T1-W, and DWI sequences independent of each other.

Table 1 Whole Body Magnetic Resonance Imaging Protocol

| Image Contrast | T1-W | DWI (b-Values 50 and 900 s/mm\(^2\)) | T2-W | T1-W (Pre- and Postcontrast) |
|----------------|------|-----------------------------------|------|---------------------------|
| Sequence       | Dixon 3-D FLASH | DW-EPI | HASTE | Dixon 3-D FLASH |
| Imaging plane  | Axial | Axial | Axial | Coronal |
| No. of slices per imaging station | 40 | 40 | 40 | 128 |
| Acquired slice thickness (mm) | 10 | 5 | 5 | 10 |
| Reconstructed slice thickness (mm) | 5 | 5 | 5 | 2.0 |
| Slice gap (mm) | 0 | 0 | 0 | 0 |
| FOV (mm) | 500 | 500 | 500 | 500 |
| Acquired voxels (mm \(\times\) mm) | 2 \(\times\) 1.6 | 3.9 \(\times\) 3.9 | 2.0 \(\times\) 2.0 | 1.9 \(\times\) 1.7 |
| Reconstructed matrix | 640 | 256 | 512 | 288 |
| Reconstructed voxels (mm \(\times\) mm) | 0.8 \(\times\) 0.8 | 2.0 \(\times\) 2.0 | 1.0 \(\times\) 1.0 | 1.7 \(\times\) 1.7 |
| Phase-encoding direction | AP | AP | AP | FH |
| TR (ms) | 6.62 | 6270 | 400 | 6.76 |
| TE (ms) | TE1 = 2.39, TE2 = 4.77 | 67 | 92 | TE1 = 2.39, TE2 = 4.77 |
| Flip angle (degrees) | 10 | 90 | 90; refocusing angle 180 | 10 |
| No. of signal averages | 1 | 2 (b50), 5 (b900) | 1 | 1 |
| Fat suppression | NA | STIR | None | NA |
| Acquisition time (per station) | 10 sec | 3 min 22 sec | 16 sec | 20 sec |

Abbreviations: AP = anterior to posterior; DW-EPI = diffusion-weighted echo planar imaging; FH = foot to head; FLASH = fast low-angle shot; FOV = field of view; STIR = short TI inversion recovery; TE = echo time; TR = repetition time; W = weighted.
References

Electronic patient records were reviewed in order to confirm whether the incidental findings detected at WBMRI resulted in further investigations, including further imaging tests and biopsy, and the final diagnosis. Where no further information was available, clinical consensus regarding the clinical significance and whether further management would have been undertaken was agreed by 2 hematologists. Clinical significance was graded as follows: unknown, low significance, moderate significance (meriting further routine investigation), and high significance (meriting urgent investigation).

Statistical Analysis

Descriptive statistics were undertaken by SPSS 24 software (IBM, Armonk, NY).

Results

A total of 348 incidental findings were detected on the T2-W sequences in 97 (97%) of 100 patients (median, 3 findings per patient; range, 1-9 findings). The most common findings are summarized in Table 2.

A total of 197 (56.6%) of 348 findings were classified as category I (benign/not clinically significant), 113 (32.5%) of 348 findings were classified as category IIA (benign and potentially clinically significant), and 38 (10.9%) of 348 findings were classified as category IIB (indeterminate and potentially malignant). There were no category III (clinically urgent) findings.

The category IIB (indeterminate) findings are summarized in Table 3 and were located at the following sites: liver (n = 7), spleen (n = 2), adrenal (n = 5), prostate (n = 5), lymph nodes (n = 5), and others (n = 14). Thirty-four patients had one indeterminate finding; 2 patients had 2 indeterminate findings; 2 patients had 3 and 4 indeterminate findings respectively.

Each additional sequence (T1-W, CE T1-W, or DWI) resulted in increased diagnostic confidence for lesion characterization compared to the initial T2-weighted imaging (Figure 1). T1-weighted Dixon sequences increased diagnostic confidence in the characterization of 12 (31.6%) of 38 findings because of its ability to demonstrate microscopic fat and hemorrhage; 5 indeterminate adrenal lesions were confirmed as adrenal adenomas with the T1-W Dixon sequences. CE T1-W sequences, only possible in 82 (82%) of 100 patients because of renal impairment in the remaining patients, increased diagnostic confidence in characterization of 16 (50%) of 32 findings compared to T2-W imaging alone and was particularly helpful for hepatic and renal lesions. DWI sequences increased diagnostic confidence in characterization of 21 (55.3%) of 38 findings compared to T2-W imaging alone. T1-weighted Dixon, DWI, and CE T1-W sequences did not improve characterization of subcentimeter pulmonary nodules.

In 16 (42.1%) of 38 patients, further investigation of indeterminate findings was recommended (further imaging 5, histology 11). Eight (50%) of 16 patients were investigated further. For the remaining 8 findings, one patient died before further investigation could be undertaken. The cause of death was progressive myeloma, and the hepatosplenic lesions likely represented extramedullary disease sites. Of the 7 findings not investigated initially, 5 of 7 findings scored as low clinical significance. Two of 7 findings were scored as moderate by clinical consensus, for whom further investigations were recommended; transvaginal ultrasound in patient 5, found to have incidental endometrial thickening, and serum prostate-specific antigen with or without histology in patient 7 with possible incidental prostatic lesion (Table 4).

No additional new malignancies were detected in this cohort. There were 3 cases of known concurrent malignancy (2 prostate cancer and 1 parotid Warthin tumor). There were also 2 cases of extramedullary plasmacytoma within lymph nodes. After exclusion of the 3 cases of known malignancy, 19 (54.3%) of 35 indeterminate findings could be fully characterized via T1-Dixon, DWI, and/or CE T1-W sequences such that no further investigations were required.

Discussion

Incidental findings are relatively common in patients with plasma-cell disorders undergoing WBMRI and were present in 97% of patients in our cohort. The majority could be characterized fully
| Indeterminate Finding (Malignancy Likelihood on T2-W Images) | T1-W | CE T1-W | DWI | Further Management Advised | Further Management Performed | Final Diagnosis or Management Recommended |
|-------------------------------------------------------------|------|---------|-----|----------------------------|----------------------------|-------------------------------------------|
| Adrenal lesion (3)                                           | II (1) | I (3) | I (3) | N                           | NA                         | Adrenal adenoma                           |
| Adrenal lesion (3)                                           | II (1) | I (3) | I (3) | N                           | NA                         | Adrenal adenoma                           |
| Adrenal lesion (3)                                           | II (1) | I (3) | I (3) | N                           | NA                         | Adrenal adenoma                           |
| Adrenal lesion (3)                                           | II (1) | I (3) | I (3) | N                           | NA                         | Adrenal adenoma                           |
| Adrenal enlargement (3)                                      | II (1) | I (3) | I (3) | N                           | NA                         | Adenomatous hyperplasia                   |
| Adrenal lesion (2)                                           | I (2) | II (3) | II (3) | Y                           | N                          | Dedicated pelvic imaging recommended; interval WBMRI demonstrated reduction in size |
| Endometrial thickening (3)                                   | II (1) | I (3) | II (1) | N                           | NA                         | Intracavitary hemorrhage                   |
| Endometrial thickening (3)                                   | I (3) | II (2) | II (2) | Y                           | Y                          | No further investigation performed         |
| Liver lesion (2)                                             | I (2) | I (2) | I (1) | N                           | NA                         | Benign cyst                               |
| Liver lesion (3)                                             | I (3) | — | II (2) | Y                           | Y                          | Hemangioma (dedicated hepatic MRI)         |
| Liver lesion (3)                                             | I (3) | II (1) | I (3) | N                           | NA                         | Hemangioma                                |
| Liver lesion (4)                                             | I (4) | II (5) | II (5) | Y                           | Y                          | Hemangioma (liver biopsy)                 |
| Liver lesion (4)                                             | I (4) | II (4) | II (4) | Y                           | N                          | Patient died before further investigation could be performed |
| Subcentimeter liver lesion (3)                               | I (3) | I (3) | I (3) | Y                           | N                          | Dedicated hepatic MRI suggested; no further imaging performed |
| Right upper lobe lung lesion, ipsilateral, mediastinal, and hilar node (3) | I (3) | — | II (4) | Y                           | Y                          | Tuberculosis with resolution of imaging findings after treatment |
| Subcentimeter lung lesion (2)                                | I (2) | I (2) | I (2) | Y                           | N                          | Stable on follow-up imaging               |
| Subcentimeter lung lesion (3)                                | I (3) | — | I (3) | Y                           | N                          | Follow-up CT chest recommended as per British Thoracic Society guidelines; no further imaging performed |
| Parotid lesion (3)                                           | II (3) | II (4) | I (3) | N                           | NA                         | Warthin tumor                             |
| Pancreatic lesion (2)                                        | I (2) | II (1) | II (1) | N                           | NA                         | Benign pancreatic cyst                    |
| Pancreatic lesion (2)                                        | I (2) | II (1) | II (1) | N                           | NA                         | Benign pancreatic cyst                    |
| Prostate lesion (3)                                          | I (3) | I (3) | II (4) | N                           | NA                         | Prostate cancer (previously diagnosed)     |
| Prostate lesion (3)                                          | I (3) | — | II (4) | N                           | NA                         | Prostate cancer (previously diagnosed)     |
| Prostate lesions (3)                                         | I (3) | I (3) | II (4) | Y                           | Y                          | Normal serum PSA; no further investigation |
| Prostate lesion (2)                                          | I (2) | I (2) | I (2) | Y                           | N                          | Correlation with serum PSA level with or without histology recommended; no further investigation |
| Prostate lesion (3)                                          | I (3) | I (3) | I (3) | Y                           | Y                          | Reviewed by urology                       |
| Renal lesion (4)                                             | I (4) | II (5) | I (4) | Y                           | Y                          | Oncocytoma (surgery)                      |
| Renal lesion (3)                                             | II (1) | II (1) | I (3) | N                           | NA                         | Hemorrhagic renal cyst                    |
| Renal lesion (2)                                             | II (1) | — | I (2) | N                           | NA                         | Hemorrhagic renal cyst                    |
| Splenic lesion (4)                                           | I (4) | II (4) | II (4) | N                           | NA                         | Patient died before further investigation could be performed |
| Perinephric thickening (2)                                   | I (1) | — | I (2) | N                           | NA                         | Perinephric hematoma                      |
| Retroperitoneal cystic lesion (3)                            | I (3) | II (2) | II (2) | N                           | NA                         | Benign nerve sheath tumor                 |
| Supraclavicular nodes (3)                                    | I (3) | II (4) | II (4) | Y                           | Y                          | Plasmacytoma                              |
Further Indeterminate Finding (Malignancy Likelihood on T2-W Images) T1-W CE T1-W DWI

| T1-W | CE T1-W | DWI | Further Management Advised | Further Management Performed |
|------|---------|-----|--------------------------|----------------------------|
|      |         |     | N                        | Y                          |
|      |         |     | Y                        | Y                          |
|      |         |     | NA                       | NA                         |
|      |         |     | NA                       | NA                         |
|      |         |     | NA                       | NA                         |
|      |         |     | NA                       | NA                         |
|      |         |     | NA                       | NA                         |

Further Management Advised: I (no improvement in diagnostic confidence), II (improved diagnostic confidence), III (requiring immediate referral).

Further Management Performed: N (no further investigation), Y (yes).

Numbers in parentheses indicate new malignancy likelihood based on that sequence.

Abbreviations: CE = contrast enhanced; CT = computed tomography; DWI = diffusion weighted; I = no improvement in diagnostic confidence; II = improved diagnostic confidence in lesion characterization; MRI = magnetic resonance imaging; NA = not applicable; PSA = prostate-specific antigen; W = weighted; WBMRI = whole body magnetic resonance imaging.

Clinical correlation and review of previous imaging was recommended as the initial action in 57% (8/14 patients) with indeterminate findings. Clinical correlation with or without cytology was recommended; no further investigation is clear, and there is growing evidence for its use in myeloma response assessment. Contrast-enhanced sequences are not used in all WBMRI protocols, particularly given the prevalence of renal impairment in this population.

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Table 4  Clinical Consensus of Significance of Indeterminate Findings

| Patient No. | Indeterminate Finding          | Further Investigation Advised                          | Investigated | Clinical Significancea |
|------------|--------------------------------|--------------------------------------------------------|--------------|------------------------|
| 1          | 5 mm subpleural lung lesion     | CT chest follow-up as per British Thoracic Society guidelines | N            | Low                    |
| 2          | 7 mm liver lesion               | Dedicated hepatic MRI                                   | N            | Low                    |
| 3          | 10 mm subpleural lung lesion    | CT chest follow-up as per British Thoracic Society guidelines | N            | Low                    |
| 4          | Endometrial thickening          | Clinical correlation with or without pelvic US          | N            | Moderate               |
| 5          | Adrenal lesion                  | Correlation with previous imaging and pelvic US        | N            | Low                    |
| 6          | Prostate lesion                 | Correlation with PSA with or without histology          | N            | Moderate               |
| 7          | SCF and cervical nodes          | Clinical correlation with or without FNA suggested       | N            | Low                    |

Abbreviations: CT = computed tomography; FNA = fine needle aspiration; MRI = magnetic resonance imaging; PSA = prostate-specific antigen; SCF = suprACLAVICULAR fossa; US = ultrasound.
aLow or moderate indicates meriting further routine investigation; high, meriting urgent investigation.
Conclusion

Incidental findings are relatively common in patients with plasma-cell disorders undergoing WBMRI. The majority of findings are benign in nature and can be characterized fully with a comprehensive protocol, necessitating few additional investigations. Our findings should provide reassurance to clinicians requesting WBMRI.

Clinical Practice Points

- There has only been one previous study assessing the frequency and significance of incidental findings at WBMRI in myeloma, in which incidental findings were detected in 38% of patients. In our study, the detection rate was significantly higher (97%). This difference may be explained by differences in imaging protocol and by variations in individual radiologist thresholds for reporting some incidental findings.
- The results of this study demonstrate that although incidental findings are common at WBMRI, most are not clinically significant. The inclusion of contrast-enhanced and DWI sequences in WBMRI protocols substantially improves reader confidence in characterization of incidental findings, thus reducing the need for further additional investigations (potentially resulting in patient anxiety and additional health care costs).
- Our results should provide reassurance to clinicians requesting WBMRI with regard to possible incidental findings, and should provide further evidence to support the inclusion of contrast-enhanced and DWI sequences in WBMRI protocols additional to their value in detection of bone disease in myeloma.

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Disclosure

The authors have stated that they have no conflict of interest.

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