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Case Report

Characterising spatial heterogeneity of multiple myeloma in high resolution by whole body magnetic resonance imaging: Towards macro-phenotype driven patient management

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ABSTRACT

Diagnosis of patients suspected of multiple myeloma requires a combination of serological and biochemical tests, bone marrow aspirate (BMA) and/or bone marrow trephine (BMT) biopsies as well as complementary information provided by whole-body cross-sectional imaging studies. However, given the heterogeneous nature of multiple myeloma, discrepancies can arise between disease burden on trephine and extent of disease within the marrow on whole-body magnetic resonance imaging (WB-MRI).

Here, for the first time, we report on a series of symptomatic multiple myeloma patients for whom there was substantial discordance between disease burden on trephine and WB-MRI.

Higher sensitivity of modern imaging techniques, such as whole-body magnetic resonance imaging (WB-MRI), provides the opportunity not only to determine skeletal involvement in multiple myeloma but also to assess tumour burden and disease activity in a large area of skeleton.

Since early 2016, the National Institute for Health and Care Excellence (NICE) has adopted WB-MRI as the modality of choice for assessing the presence of myelomatous disease as well as evaluation of its burden in suspected smouldering and symptomatic multiple myeloma patients [1]. More recently, the International Myeloma Working Group (IMWG) updated guidelines recommending WB-MRI as "complementary" to whole-body low-dose computed tomography (WBLDCT) for suspected smouldering myeloma patients with negative or inconclusive WBLDCT scans; and for suspected multiple myeloma patients with inconclusive WBLDCT [2]. The sensitivity and detection rate of WB-MRI for delineation of multiple myeloma bony deposits is higher than WBLDCT [3] and ^{18}F-labeled fluoro-2-deoxyglucose computed tomography (^{18}F-FDG-PET-CT) [4] and unlike WBLDCT and ^{18}F-FDG-PET-CT, WB-MRI does not involve use of ionizing radiation. NICE also reported that WB-MRI showed the largest rise in incremental quality of life adjusted years which was heavily influenced by it being assigned the most sensitive imaging technique [1]. WB-MRI also offers the advantages of assessing disease which may be threatening the spinal cord and differentiation of benign from malignant vertebral fractures [5]. Furthermore, WB-MRI alongside ^{18}F-FDG-PET-CT are currently the mainstay imaging techniques capable of providing functional assessment of bone disease at baseline and following therapy. As such, WB-MRI protocols combining functional imaging techniques such as diffusion-weighted (DW)-MRI are being increasingly advocated for response monitoring following chemo/radiotherapy in patients with symptomatic multiple myeloma [6,7]. This has been reflected in NICE guidelines for investigating disease progression and disease relapse in multiple myeloma where WB-MRI has been recommended for myeloma patients with serological evidence of relapse or disease progression [1].

In addition to radiological investigations, the diagnosis, response assessment and assessment of disease relapse/progression of symptomatic multiple myeloma patients is made on the basis of serological investigations, immunofixation electrophoresis of blood serum/urine samples and bone marrow aspirate (BMA) and bone marrow trephine (BMT) biopsies [2,8]. According to the IMWG criteria, demonstration of clonal bone marrow plasma cells $\geq$10% by either BMA or BMT biopsy is required in addition to a 'myeloma defining event' for the diagnosis of multiple myeloma [8]. In post-treatment settings, the criteria for "complete response" and "minimal residual disease -negative" status requires "low plasma cell count" and "no measurable plasma cell" in the bone marrow, respectively [2]. However, bone marrow biopsy

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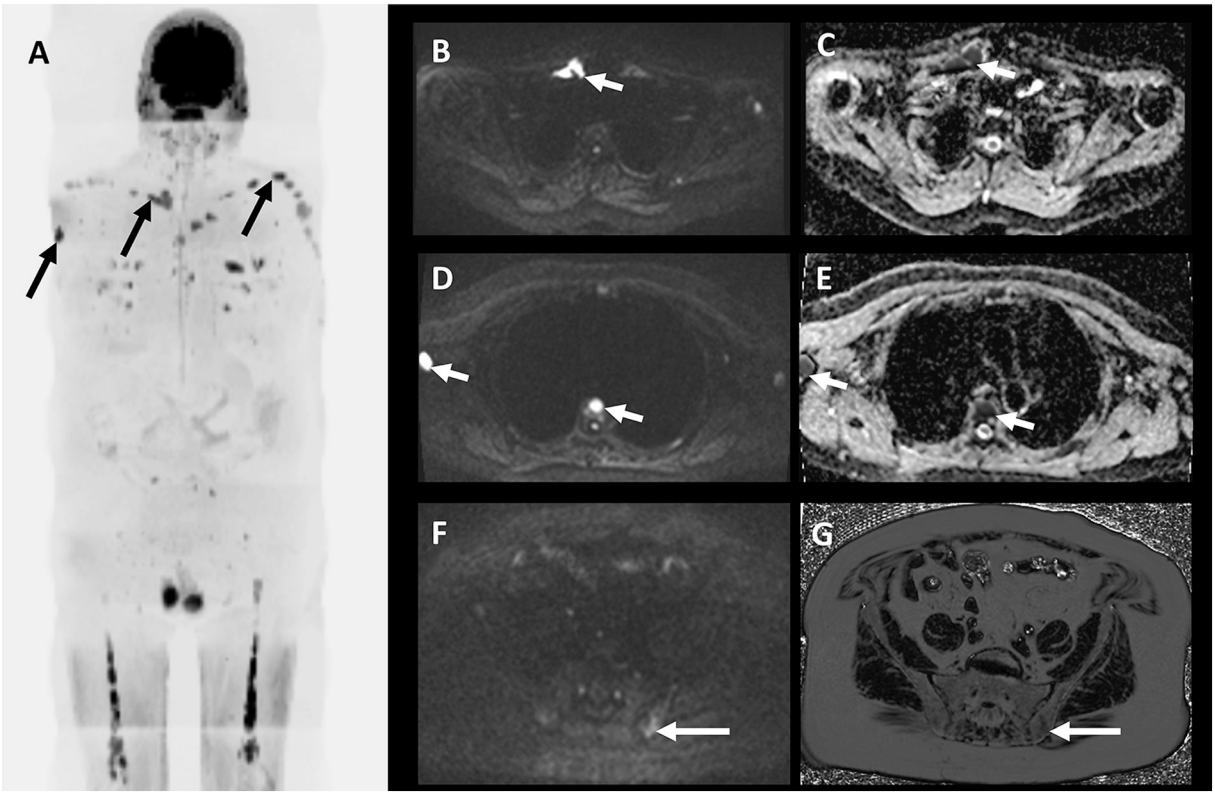

Fig. 1. Trephine underestimates disease burden at diagnosis.
Whole-body MRI of a 74 year old man who presented with widespread musculoskeletal pain and serum paraprotein (IgG kappa) of 15 g/l. Bone marrow aspirate (BMA) of the left posterior iliac crest was reported normal with no malignant plasma cell detected and no clonal plasma cells by flow cytometry. Bone marrow trephine biopsy (BMT) was negative for malignant plasma cell with CD138 and CD38 positive and Cyclin D1 and CD 56 negative and no light chain restriction. Subsequent whole-body MRI scan demonstrated widespread multifocal disease (A-G). There was evidence of multifocal myelomatous lesions on three-dimensional (3D) maximum intensity projection (MIP) inverted-scale whole-body diffusion weighted imaging (A)(*b*-value 900 s/mm^2). Focal lesions on diffusion weighted imaging and corresponding apparent diffusion coefficient maps are shown for right clavicle (B and C), thoracic spine and right humerus (D and E). The bone marrow biopsy/trephine tract passing through normal marrow is evident on diffusion weighted imaging (F) and fat-fraction map (G) of left posterior iliac crest (arrows). CT-guided biopsy of the right clavicle head and sternal lesion confirmed plasma cell (100%) myeloma with CD138, CD38 and MUM1 positive, and kappa light chain restriction. There was aberrant co-expression of cyclin D1 but not CD56.

interpretation is prone to caveats. For instance, bone marrow sampling by aspirate or trephine frequently produces significantly different estimations of the level of plasma cells, with the trephine usually yielding an appreciably higher percentage [9]. Variation in sampling is also observed due to heterogeneous distribution of focal disease and patchy plasma cell distribution on BMA or BMT preparations could also be subject to inter-observer variability [10].

Given that the majority of patients with multiple myeloma develop bone disease, a thorough and accurate assessment of the degree of skeletal involvement using bone marrow samples as well as cross-sectional imaging is of utmost importance. Whole-body imaging techniques such as WB-MRI have revealed that multiple myeloma does not always affect mineralised bone and bone marrow in a homogeneous way [2]. In fact, evidence suggests that more than half of patients with multiple myeloma have plasma cell accumulation and bone destruction occurring in a focal or patchy way [2].

Figs. 1–3 illustrate examples of 6 multiple myeloma patients at different stage of their management where considerable discrepancies between WB-MRI and routine BMT assessments were reported.

The ability to identify discrete areas of diffuse versus focal plasma cell infiltration by sensitive imaging techniques such as WB-MRI provides a novel dimension for detecting and evaluating disease burden and monitoring treatment response. To date, in most cases at initial diagnosis, genetic testing for risk assessment and definition of complete remission and minimal residual disease assessment in multiple myeloma has relied on plasma cell percentage and bone marrow specimen biology, which are taken blindly, mainly from the iliac crest [2]. However, posterior iliac crest biopsy samples are not always representative of the real disease burden because the biopsy might either hit or miss a focal lesion and thereby overestimate or underestimate the plasma cell percentage in bone marrow. This is clearly illustrated in the example case provided in Fig. 1. Whilst left posterior iliac crest bone marrow aspirate and trephine biopsies showed no malignant plasma cells, CT-guided targeted biopsy of the clavicle head and sternal focal lesions, evident on WB-MRI, confirmed plasma cell infiltration of bone marrow.

In a study by Rasche et al. [11], it has been shown that in some patients, genomic findings of multiple myeloma cells from a random sample and an image-guided biopsy of a focal lesion can be different. In another prospective study, Hillengass et al. [12] have shown that the plasma cell percentage differs significantly between random bone marrow biopsy and biopsy targeting osteolytic lesions. They showed that median plasma cell infiltration of random iliac crest trephine sampling was 30% (range 0–90%) compared to median of 60% (range 0–100%) for CT-guided biopsies. Given the level of existing heterogeneity across the skeleton and its potential influence on clinical management, more comprehensive bone marrow imaging would be highly desirable in multiple myeloma.

Traditionally, response evaluation in multiple myeloma has been based on the assessment of serum and urine monoclonal protein concentrations via protein electrophoresis or immunofixation, or both, allowing for the detection of trace amounts of paraprotein as a marker of tumour burden. This was subsequently complemented by addition of

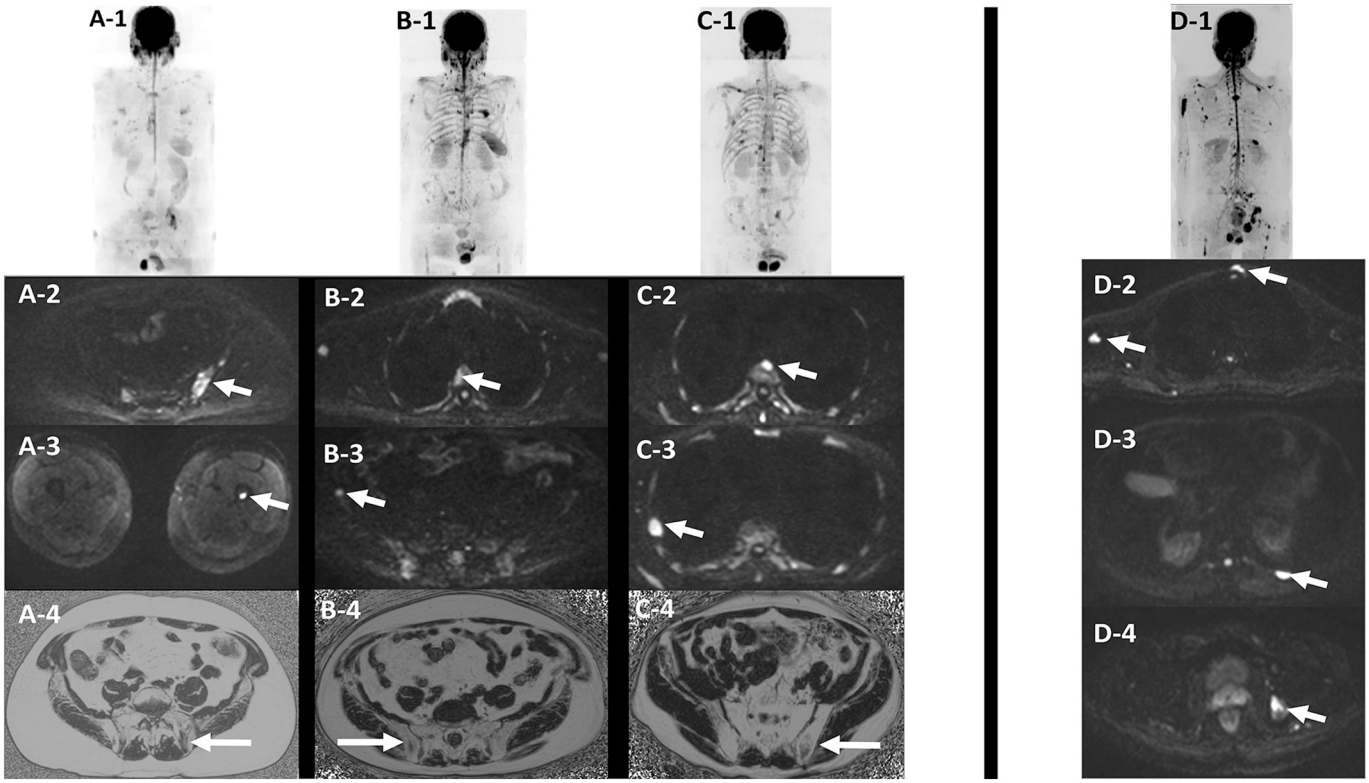

Fig. 2. Trephine underestimates disease burden at relapse.

Panel A: WB-MRI of a 51 year old man diagnosed with kappa light chain myeloma in 2015. At suspected relapse in 2018 kappa light chains were recorded as 705 mg/l (nadir 92 mg/l). BMT was performed on the posterior inferior iliac crest and showed no significant increase in numbers of plasma cells (not exceeding 2–3%). However there was evidence of multifocal myelomatous lesions on three-dimensional (3D) maximum intensity projection (MIP) inverted-scale whole-body diffusion weighted imaging (A-1)(*b*-value 900 s/mm^2). Images show a 6 cm left iliac bone lesion (A-2) and a 5 mm focal lesion in proximal left femur (A-3) on diffusion weighted imaging (*b*-value 900 s/mm^2). The left posterior iliac crest trephine tract is evident on fat-fraction map directly above and missing the described left iliac bone lesion (A-4).

Panel B: WB-MRI of a 59 year old man diagnosed with IgA kappa multiple myeloma and treated to partial response followed by high dose Melphalan autologous stem cell transplant. On follow-up, 1 year post-transplant, the patient presented with non-specific pains and serum biochemistry showed very low-level biochemical relapse (Paraprotein of 2 g/l). Bone marrow trephine showed only 5% plasma cells. However there was evidence of multifocal myelomatous lesions on three-dimensional (3D) maximum intensity projection (MIP) inverted-scale whole-body diffusion weighted imaging (B-1)(*b*-value 900 s/mm^2). Examples of focal lesions in T4 vertebral body (B-2) and anterior right iliac crest focal lesion (B-3) are shown on diffusion weighted imaging (*b*-value 900 s/mm^2). The right posterior iliac crest trephine tract sampling normal appearing marrow is evident on fat-fraction map (B-4).

Panel C: WB-MRI of a 56 year old man who presented with left axillary lymphadenopathy in 1991. He was confirmed of having stage IA nodular lymphocyte predominant Hodgkin's lymphoma and was treated with local radiotherapy. At suspected second relapse in 2015 multiple lytic lesions were noted on staging investigations. Serum biochemistry showed IgM lambda paraprotein of 19 g/l. Bone marrow aspirate showed 7–8% plasma cells and bone marrow trephine showed 10% plasma cells. There was evidence of extensive multifocal myelomatous lesions on three-dimensional (3D) maximum intensity projection (MIP) inverted-scale whole-body diffusion weighted imaging (C-1)(*b*-value 900 s/mm^2).

Examples of focal lesions in vertebral body of thoracic spine (C-2) and right rib (C-3) are shown on diffusion weighted imaging (*b*-value 900 s/mm^2). Post-radiotherapy marrow changes seen in pelvis and therefore biopsies may not have been representative of disease elsewhere. The left posterior iliac crest trephine tract is evident on fat-fraction map through marrow, which appears disease free (C-4).

Panel D: WB-MRI of a 54 year old man diagnosed with Kappa light chain myeloma in 2012.

At suspected 3rd relapse in 2018 Kappa light chains increased to 26 mg/l. There was evidence of extensive multifocal myelomatous lesions on three-dimensional (3D) maximum intensity projection (MIP) inverted-scale whole-body diffusion weighted imaging (D-1)(*b*-value 900 s/mm^2). Focal disease in the sternum and right humerus (D-2), left rib (D-3) and left pelvis (D-4) is shown on diffusion weighted imaging (*b*-value 900 s/mm^2). Right posterior iliac crest trephine was performed subsequent to MRI and showed extreme hypocellularity (5%), increased reticulin and marrow aplasia.

quantitation of bone marrow plasma cells on BMT or BMA, serum free light chain (sFLC) assays and immunohistochemical clonal assessment on trephine biopsies. However, as acknowledged by IMWG, most patients even with deep response relapse following treatment, highlighting persisting disease that is undetectable by recommended response-monitoring techniques [13].

Conversely, and for the first time, the most recent IMWG guidelines on criteria for assessment of treatment response in multiple myeloma takes into account and recommends the additional value of the information derived from whole-body imaging [13].

Minimal residual disease negativity (MRD-negative) is defined by no measurable plasma cell in the bone marrow (by sequencing or flow cytometry), with stringent complete response defined as absence of clonal cells in bone marrow biopsy by immunohistochemistry and complete response as <5% plasma cells in bone marrow aspirates [13]. However, as with initial evaluation, most of the bone marrow sampling is performed in the pelvic bone, due to its relatively easy accessibility. As such, residual disease at other sites not sampled by iliac crest biopsy could remain undetected.

Hillengass et al. showed that following ASCT, the number of focal lesions on post-treatment WB-MRI was informative for survival outcome with good concordance between serological response and post-treatment imaging changes [14].

The results from several studies investigating WB-MRI and ^{18}F-FDG-

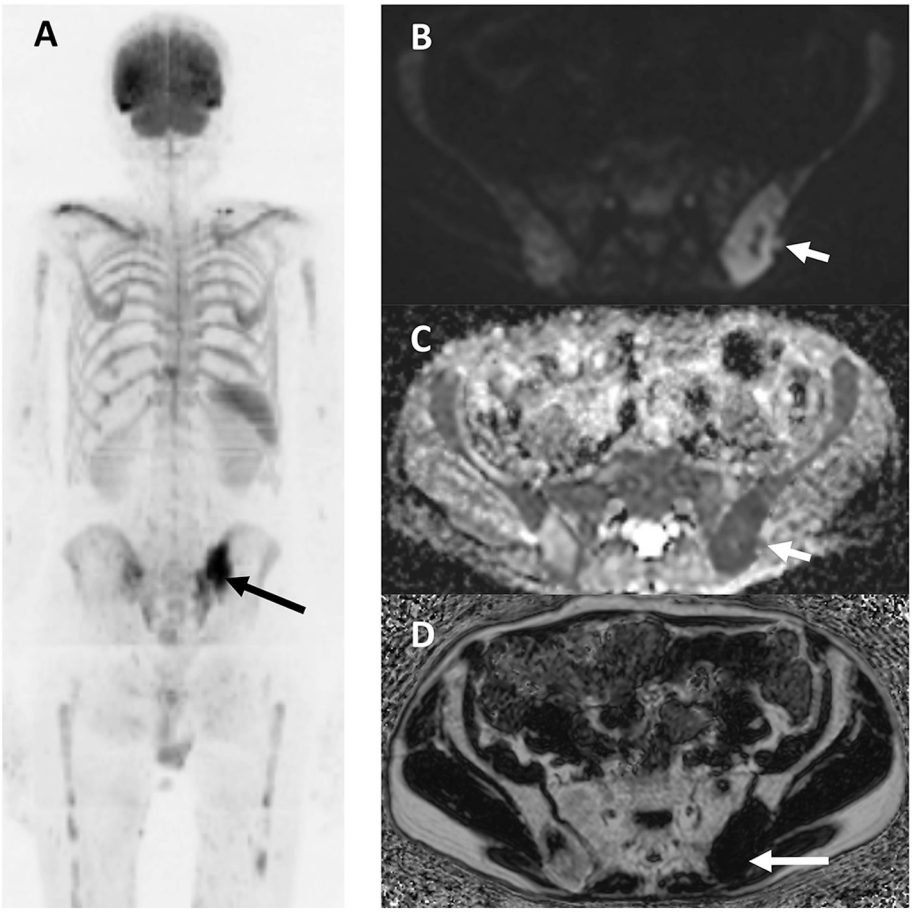

Fig. 3. Trephine overestimates disease burden. WB-MRI of a 69 year old man having routine bone marrow trephine to assess response 1 year post transplant- bone marrow trephine showed 90% infiltration with plasma cells however paraprotein level and all other serological and biochemical tests were normal. Subsequently, the patient was imaged with WB-MRI to evaluate the extent of possible relapsed multiple myeloma. There was evidence of a single myelomatous lesion on three-dimensional (3D) maximum intensity projection (MIP) inverted-scale whole-body diffusion weighted imaging (A)(*b*-value 900 s/mm^2) (arrow). The same lesion is shown on diffusion weighted imaging (*b*-value 900 s/mm^2)(B), apparent diffusion coefficient map (C) and fat-fraction map (D). Inadvertent sampling of the solitary 6 cm single focus of marked restricted diffusion in left posterior iliac crest was considered as an overestimation of overall bone marrow plasma cell percentage.

PET-CT as response monitoring tools are noted in the updated IMWG guidelines which for the first time has incorporated a category of IMWG MRD criteria denoted as "imaging (^{18}F-FDG-PET-CT) plus MRD-negative" category.

The important information provided by WB-MR imaging in post-treatment settings is highlighted in Figs. 2 and 3 with examples of underestimations and overestimation of disease, respectively. These examples emphasise the potential and important role that whole-body imaging, including WB-MRI, could play not only for initial evaluation, but also, for response monitoring in patients with multiple myeloma. Furthermore, it is shown that extramedullary and asymptomatic disease relapse with insidious increase in serum monoclonal protein are being increasingly observed following autologous stem cell transplant (ASCT) and/or treatment with novel agents [15,16]. Considering the evolving patterns of relapse in era of novel agents, and given that the nature of myeloma changes over time, the role of imaging including WB-MRI might be more pertinent for accurate monitoring of patients following therapy.

It should be noted that in our centre we have implemented WB-MRI for baseline assessment and post-treatment monitoring of multiple myeloma patients. MRI capacity limitations have led to inconsistent and variable uptake at other centers and for some patients with severe claustrophobia or MRI incompatible devices, MRI may be unsuitable. It remains to be seen whether WBLDCT and/or ^{18}F-FDG-PET-CT could provide findings comparable to those described in this series. Nevertheless, we believe with the advent of functional imaging techniques, ongoing development and standardization of quantitative imaging biomarkers and a more widespread availability of modern imaging platforms, the complementary information provided by whole-body imaging could be further evaluated and implemented into everyday clinical practice in order to refine management strategies for individual patients.

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