European Journal of Radiology 83 (2014) 970–974

Contents lists available at ScienceDirect

European Journal of Radiology

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

Infiltration patterns in monoclonal plasma cell disorders: correlation of magnetic resonance imaging with matched bone marrow histology

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ARTICLE INFO

Article history:
Received 19 August 2013
Received in revised form 27 February 2014
Accepted 7 March 2014

Keywords:
Paraproteinemias
Multiple myeloma
Plasma cells
Magnetic resonance imaging
Bone marrow
Histology

ABSTRACT

Objectives: To investigate how plasma cell infiltration patterns detected by MRI match the plasma cell distribution in bone marrow biopsy.
Methods: We assessed 50 patients with monoclonal plasma cell disorders of all clinical stages. MRI infiltration pattern was compared with matched BM histology from the same anatomic region.
Results: MRI revealed a minimal ($n = 11$, 22%), focal ($n = 5$, 10%), diffuse ($n = 14$, 28%) and mixed ($n = 20$, 40%) infiltration pattern. Diffuse MRI pattern was predominant in smoldering myeloma patients whereas the MRI patterns with "focal component" (i.e. focal and mixed) were most common in symptomatic myeloma ($p < 0.01$). In histology an interstitial ($n = 13$, 26%), nodular ($n = 23$, 46%) and packed marrow ($n = 14$, 28%) was found respectively. All three histological types of infiltration were observed in patients with diffuse and mixed MRI patterns. Minimal MRI pattern was found in all MGUS patients and was associated with an interstitial BM infiltration. In two patients with minimal MRI pattern an extensive micro-nodular BM infiltration was found in histology.
Conclusions: Infiltration patterns in MRI represent different histological growth patterns of plasma cells, but the MRI resolution is not sufficient to visualize micro-nodular aggregates of plasma cells.

1. Introduction

Multiple myeloma (MM) is an incurable neoplastic disorder characterized by the infiltration and proliferation of monoclonal plasma cells in bone marrow (BM). According to a current disease progression model [1–3] the symptomatic disease is preceded by preclinical stages of monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM). The number of neoplastic plasma cells in the bone marrow gradually increases with disease progression. However, the distribution of plasma cells within the bone marrow is irregular. As described by Bartl et al. [4], 6 different microscopic infiltration patterns, ranging from interstitial infiltration to packed marrow, can be found in bone marrow biopsies.

Due to uneven distribution of plasma cells various infiltration patterns (minimal, focal, diffuse, mixed) are also observed by modern imaging techniques [5,6]. Magnetic resonance imaging (MRI) is the most sensitive method for detection of both focal and diffuse infiltrates [6]. In contrast to histology, MRI patterns represent "macroscopic" aggregates of plasma cells and differ from histological patterns in scale by an order of magnitude. Nevertheless, MRI patterns correlate significantly with the number of plasma cells in the bone marrow [5] and provide important information for patient management [7,8]. Even thought the infiltration patterns in the biopsy as wells as in imaging are widely used in daily clinical practice, no direct comparison of histological and imaging infiltration patterns has been performed yet.

The aim of the present work was to investigate how infiltration patterns detected by MRI match the plasma cell distribution as seen in bone marrow biopsy. For this, we performed a detailed comparison of an MRI of the pelvis with almost synchronous bone marrow histology from the same anatomic region in a cohort of patients with different stages of monoclonal plasma cell disorders.

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http://dx.doi.org/10.1016/j.ejrad.2014.03.005
0720-048X/

Table 1
Patient characteristics.

Median age, years (range)	57	(38 74)
Sex, *n* (%)		
Male	24	(48)
Female	26	(52)
IMWG Category, *n* (%)		
MGUS	4	(8)
SMM	19	(38)
MM	27	(54)
Ig Isotype, *n* (%)		
Asecretory	1	(2)
IgG	37	(74)
IgA	8	(16)
BJ	4	(8)

IMWG, international myeloma working group; BJ, Bence Jones protein.

2. Materials and methods

2.1. Patient characteristics

The current group of 50 patients with monoclonal plasma cell diseases consisted of 4 individuals with monoclonal gammopathy of undetermined significance (MGUS), 19 patients with smoldering multiple myeloma (SMM) and 27 patients with symptomatic multiple myeloma (MM) according to the classification of the international myeloma working group [9]. Of the 27 patients with MM 3 were symptomatic because of anemia, 3 because of anemia and bone disease and 21 because of bone disease alone. Patient characteristics are summarized in Table 1.

2.2. Magnetic resonance imaging

All whole-body MRI scans from which the pelvic images were used for the current analysis were performed at the University Hospital of Heidelberg and the German Cancer Research Center, Heidelberg, Germany on one of two similar 1.5 Tesla MRI systems (MAGNETOM Avanto, Siemens Medical Solutions, Erlangen, Germany) according to a protocol published previously [10,11]. Focal lesions were defined as lesions 5 mm (slice thickness of the MR images) or larger in diameter with low signal intensity in T1-weighted and corresponding high signal intensity in T2-weighted images (Fig. 1a). Diffuse infiltration was defined as homogeneously reduced signal intensity detectable in T1-weighted images alone or in combination with increased signal intensity in T2-weighted images according to the definitions published previously [12,13]. This retrospective analysis of MR images, histology and clinical parameters was approved by the institutional ethics committee. Due to the retrospective nature of the analysis, an informed consent was waived. Both examinations had been performed for clinical work-up. Investigators were blinded to clinical parameters and stage of the disease.

2.3. Evaluation of imaging parameters

Radiological review was performed by two investigators in consensus (JH, TB). Infiltration patterns were classified according to the definitions by Stäbler et al. [13] as minimal (homogeneous hyperintensity in T1- and hypointensity in T2-weighted images, i.e. similar appearance as normal bone marrow), diffuse (homogeneous hypointensity in T1 alone or in combination with hyperintensity in T2-weighted images compared to intervertebral discs) or focal (hypointense lesions in T1- on a hyperintense background corresponding to hyperintense lesions on a hypointense background in T2-weighted images). A mixed pattern was defined as focal lesions on a diffuse background. Examples of the different infiltration patterns are shown in Fig. 1A.

2.4. Bone marrow samples

The matched bone marrow biopsies were taken directly after the MRI in 48 patients. In two patients the biopsies were taken 19 days before and 20 days after the MRI, respectively. A subset of the biopsies ($n = 22$) was fixed in formol–methanol solution, embedded in methacrylat as described previously [4]. The remaining core biopsies were fixed in 4% buffered formaldehyde and embedded in paraffin according to standard histology protocols. 3–4 μm thin sections were cut and stained for Giemsa to evaluate the histological infiltration pattern. To confirm the accuracy of histological pattern evaluation the paraffin embedded biopsies were additionally immunostained for CD138 as described previously [14].

2.5. Evaluation of histological parameters

The histological infiltration pattern was classified as (1) interstitial, (2) interstitial and sheet-like, (3) interstitial and nodular, (4) nodular, (5) sarcomatoid and (6) packed marrow as described [15]. To facilitate the comparative analysis histological patterns were grouped as follows: the cases with exclusively interstitial infiltration were classified as “interstitial”, the cases with interstitial and sheet-like or nodular infiltration were grouped into the category “nodular”, cases with sarcomatoid infiltration pattern and packed marrow were grouped into the category “packed marrow”. The bone marrow cellularity and the number of plasma cells were assessed in a semi-quantitative manner as described [16]. The histological analysis was performed by an experienced haematopathologist (MA) who was blinded to clinical and imaging data. Examples of histological infiltration patterns are depicted in Fig. 1A.

2.6. Statistical analysis

All analyzes were conducted in R [17]. The plots were generated using ggplot2 library [18]. For analysis of discrete variables the Chi-square or Fishers exact test was employed. The comparison of continuous variables was performed using Mann–Whitney U test.

3. Results

3.1. Imaging findings

A minimal pattern was found in 11 patients (22%), a focal pattern in 5 patients (10%), a diffuse pattern in 14 patients (28%) and a mixed pattern in 20 patients (40%). All 4 MGUS patients showed a minimal infiltration in MRI. However, 3 patients with SMM and also 4 patients with symptomatic myeloma presented with a minimal pattern. Examples of infiltration patterns in MRI are shown in Fig. 1A (upper and middle row).

3.2. Histological findings

Histology revealed an interstitial pattern in 13 patients (26%), nodular infiltrates in 23 patients (46%) and packed marrow in 14 patients (28%). The length of bone marrow biopsies was highly variable and ranged from 1 mm to 30 mm (median = 15 mm). Importantly, the biopsy size was not different among the three histological patterns, so it is unlikely that the assessment of histological pattern was biased by sampling error due to small biopsy size (Fig. 2a). The amount of fatty marrow was not different in cases with interstitial and nodular infiltration, but significantly reduced in cases with packed marrow (Fig. 2b). The number of plasma cells was significantly associated with histological infiltration pattern (Fig. 2c).