Superiority of Magnetic Resonance Imaging Over Conventional Radiographs in Multiple Myeloma

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Abstract. *Background: Bone lesions in multiple myeloma (MM) are screened with radiological skeletal survey (RSS) due to its widespread availability. Although bone lesions can be missed by RSS, more sensitive radiological surveys are not as yet recommended for routine use due to the low availability of the methodology and economical considerations. Case Report: We report on a 68-year-old male with IgG kappa stage IIIA MM presenting with skeletal pain, fatigue and osteolytic lesions. Since the patient refrained from more intensive therapy, including autologous stem cell transplantation (auto-SCT), he was treated with vertebral irradiation and included in an institutionally guided study which randomized melphalan, prednisone (MP)-lenalidomide (MPR) to MP alone. Although he initially responded, his bone pain reoccurred after three MP cycles. The repeated RSS showed minor, if any changes. Therefore, an MRI was added which revealed extensive osteolyses and extramedullary disease. Justified by these results it was possible to convince the patient that a more intensive therapy approach, including auto-SCT, local irradiation and thalidomide maintenance, was appropriate. Conclusion: This case calls for an earlier integration of MRI and/or PET/CT scanning in MM, even if RSS remains unchanged, especially if initial bone disease is substantial and/or MM-related symptoms recur. The time course of information and linked decision-making point towards the future significance of an intensified integration of imaging methodologies in the classification and disease management of MM.*

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Osteolytic lesions are frequently observed in multiple myeloma (MM) patients and have, as hallmark of the disease, been included in guiding treatment initiation within the CRAB criteria (hypercalcemia, renal impairment, anemia, bone disease) (1-3). Bone lesions are routinely screened by performing a radiological skeletal survey (RSS), which still remains the 'gold' standard of the staging procedure due to its widespread availability, low cost and reasonable time demand. However, the sensitivity is significantly lower, if compared to cross-sectional or functional imaging techniques, such as computed tomography (CT), magnetic resonance imaging (MRI) and 2-deoxy-2[F-18]fluoro-D-glucose positron emission tomography (FDG-PET) scanning (3, 4). Albeit considered as widely used in myeloma by most experts, more sensitive radiological surveys are not as yet recommended for routine use, due to the low availability of the methodology and economical considerations (3, 4). At our center, consistent with many others worldwide, RSS is the initial diagnostic procedure performed with MM work-up, whereas MRI is performed with reoccurrence of skeletal symptoms, with discrepancy in RSS results, in emergency situations, such as cord compression, or within clinical trials (3).

Case Report

We report on a 68-year-old gentleman who was admitted to our Medical Center in 3/2007 due to skeletal pain and fatigue. Blood sample testing showed the results as displayed in Table I. The RSS and externally performed body-CT revealed osteolytic lesions within his pelvis and vertebrae, correlating with 60% bone marrow (BM)-infiltrating plasma cells (PCs). Cytogenetic and Fluorescent *in situ* hybridization (FISH) analysis was performed on purified BM PCs, but was not informative due to few PCs being obtained. The patient was diagnosed with an IgG kappa (κ) MM, stage IIIA according to Salmon and Durie (ISS stage II; Table I). The patient's comorbidities included essential arterial hypertension and

Table I. *Patient characteristics and MM-specific changes during MM progression and therapy.*

MM parameter	Time course					
	3/2007	6/2007	8/2007	12/2007	6/2008	9/2008
MM classification D&S IIIA,ISS II	ID IgGκ MM					
MM response		SD	1. PD	vg PR	2. PD	3. PD
Hemoglobin (g/dl) [12-18]	8.7	11	10.4	13.3	9	7.6
Total protein (g/dl) [6.4-8.3]	12.7	8.7	9.1	7.1	10.7	8.3
IgG (g/dl) [<16]	90	31.4	36.1	9.2	55.1	17.9
Kappa (κ) LC (mg/dl)* [<19.4]	41	32.9	43	12	87	149
LDH (U/l) [135-225]	226	190	292	172	2349	1131
β2-MG (mg/l) [0.8-2.2]	3.8	3.2	3.6	1.9	17.3	8.1
BM infiltration PCs (%)	60	ND	25	3	20	20
BM karyotype (FISH)	Not informative	NE	Trisomy 11, tetrasomy 9	NE	NE	NE
PB PCs (%)	0	0	0	0	15	5
RSS	Osteolytic lesions: pelvis + vertebrae	No change	No change	No change	No change	No change
CT[1] / MRI[2]	[1]Disseminated osteolyses	NE	[2]Osteolyses, massive BM infiltration, EM sites	[2]No EM sites	[2]PD EM sites	[2]Further PD EM sites
EM MM sites	Not at ID	NE	Multiple abdom. sites	No EM sites	PD EM sites: abdom., pulmon., pleural, LN	PD EM
Anti-MM therapy	HD-Dex, local irradiation, MPR *vs*. MP-alone-study	3 Cycles MP	Auto-PBSCT	Thal	Cyclo/Dex/Bort, 3 cycles	Len/dex 2 Weeks before pt's death:BSC

Pt: Patient, MM: multiple myeloma, ID: initial MM diagnosis, D&S: Durie and Salmon classification, ISS: international staging system, κ: kappa light chains, *serum free light chain by Freelite kit determination, FISH, fluorescent in situ hybridization, SD: stable disease, vg PR: very good partial remission, PD: progressive disease, CR: complete response (EBMT criteria), NE: not evaluated, EM: extramedullary MM sites (assessed by MRI), abdom abdominal, pulmon pulmonary, LN lymph nodes, RSS: radiological skeletal survey, MRI: magnetic resonance imaging, BM: bone marrow, PB: peripheral blood, HD-Dex: high-dose dexamethasone, MPR: MP-Lenalidomide, MP: melphalan/prednisone, auto-PBSCT: autologous peripheral blood stem cell transplantation, Thal: thalidomide maintenance, Cyclo/Dex/Bort: cyclophosphamide, dexamethasone, bortezomib; Len/dex: Lenalidomide/dexamethasone, BSC: best supportive care due to pt's preference/wish.

being considerably overweight (BMI 30 kg/m^2). After informed consent, the patient was immediately treated with high-dose dexamethasone, localized vertebral irradiation and since he refrained from intensive therapy, such as autologous peripheral blood stem cell transplantation (auto-PBSCT), he was included in an institutionally guided study which randomized melphalan/prednisone (MP)-lenalidomide (MPR) to MP alone (internal study #554).

Within the MPR study, the patient was randomized to MP and initially responded, showing substantial relief of his initial symptoms (bone pain, night-sweat, fatigue), increase in his hemoglobin and decrease in his total protein (TP) and IgG-levels (6/2007; Table I). Nevertheless, after three MP cycles, he showed recurring bone pain. He was readmitted to our hospital and a diagnostic work-up was repeated. Since at that time, the TP and IgG had slightly increased (Table I), the RSS was repeated. This showed no changes, whereby the magnified view of his right hip suggested minor, if any, progression of his osteolytic lesions at the right femur and its large tubercle (Figure 1A, B). Since the reoccurrence of bone pain was contradicted only by subtle changes in the RSS, an MRI was added, which overtly demonstrated osteolysis of the right hip by extensive signal alterations in non-contrast-enhanced T1-weighted (T1w) and T2w sequences (Figure 2), massive BM infiltration, and soft tissue extramedullary disease. The extensive osteolytic lesion of the pelvis was assessed three days later by repetition of the plain x-ray, which was still not able to reproduce the patient's substantial osteolyses (Figure 1C).

Of note was that, consistent with his initially decreasing TP and IgG, the BM PC infiltration had decreased from 60% (3/2007) to 25% (8/2007; Table I). BM sections revealed still densely infiltrating, bi- and multinucleated PCs (Figure 3A), which proved to be κ positive (Figure 3B). *Via* histology, notable osteolytic features, with predominant osteoclasts (Figure 3C) and bone-infiltrating and bone-destructive PCs (Figure 3D) were detected (1). BM FISH analysis was repeated and revealed trisomy 11 and tetrasomy 9, but no deletion of chromosome 13, deletion of 17p13 (p53) or detection of t(4;14), t(11;14) or t(14;16) (Table I).

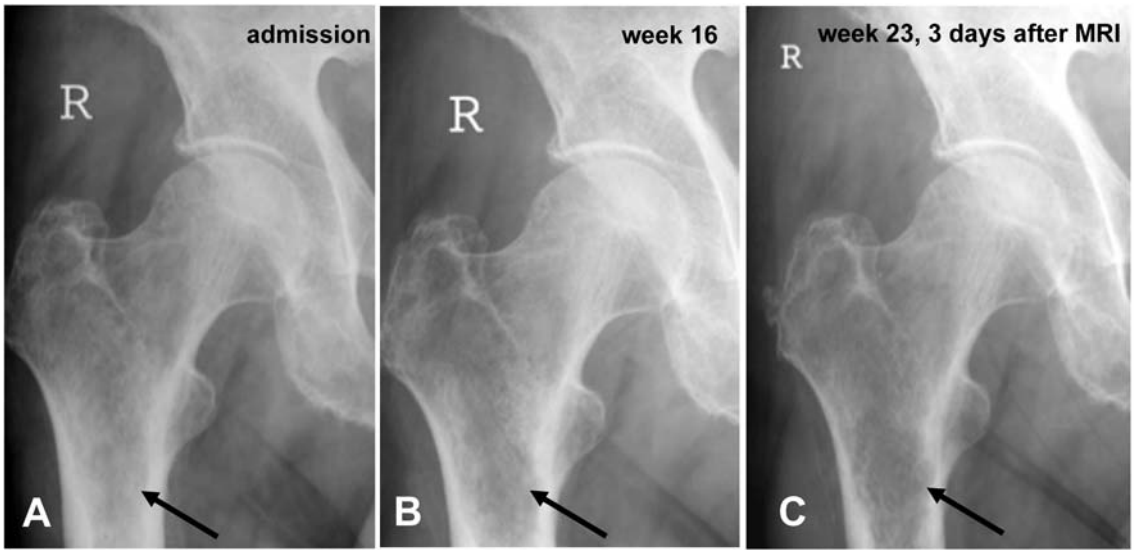

Figure 1. *Radiological skeletal survey at initial presentation in 3/2007 (A), on recurrence of bone pain in 8/2007 (B) and after MRI (C). Osteolytic changes did not appear to be substantial at these times.*

Due to these findings, more intensive anti-myeloma treatment with auto-SCT was again offered to the patient, now consented to by him and his family. He received intravenous etoposide (360 mg/m^2), cyclophosphamide (1500 mg/m^2) and epirubicine (75 mg/m^2) (EVC). Peripheral blood stem cells were harvested after the 2nd EVC cycle and an auto-PBSCT (melphalan 200 mg/m^2 conditioning) was performed, thereby achieving a very good partial remission (vgPR). Pelvic (right hip) irradiation was performed for consolidation and due to the patient's aggressive bone destruction and only one PBSCT being performed (instead of two), low-dose thalidomide (100 mg/day) and prednisone (50 mg every 2nd day) maintenance was begun to further stabilize the obtained response (5). This was performed according to recent recommendations suggesting that thalidomide will elongate time to treatment failure, avoid early reinduction of anti-MM agents and may be equally effective as tandem-PBSCT upfront (5).

The patient course was complicated due to progression 10 months after auto-PBSCT: extramedullary sites recurred, peripheral blood PCs were 15%, whereas BM PCs remained at 20%. Despite anti-MM therapy with cyclophosphamide, dexamethasone and bortezomib (6), the response remained short-lived and progression persisted. Despite also use of lenalidomide and dexamethasone, κ-serum free light chains increased, whereas his IgG levels remained low. This disease evolution, induced with longer disease duration and/or extensive treatment, showing changes in the biological behaviour of MM and unusual relapse emergence, with a shift in secretion from intact immunoglobulins to free light chains only has recently been described by our group in the largest to date series of 10 patients (7). Our patient eventually died due to extramedullary progression 18 months after initial diagnosis (Table I).

Discussion

Plain radiographs and RSS are used for myeloma staging as this diagnostic strategy permits an easy clinical staging which correlates well with myeloma cell mass and prognosis (3, 4). Both screening tools are widely used, but often have negative results in MM patients who have extensive lytic lesions and offer little in the follow-up of bone disease. Appropriate use of imaging techniques is essential in the identification and management of skeletal complications and involves determination of the extent of intramedullary bone disease, detection of extramedullary foci, identification and characterisation of complications and evaluation of the extent and progression of the disease. The availability of more sensitive imaging techniques has led to the more frequent use of CT, MRI and PET scanning (8). These imaging tools supplement standard radiographs, since plain x-ray can only detect osteolytic lesions if more than 50% bone loss has occurred. MRI can provide information complementary to the skeletal survey and is recommended in MM patients with normal conventional radiography and in patients with an apparently solitary plasmacytoma of bone (8). In approximately 20% of patients with negative X-rays, CT, MRI and PET show evidence of active myeloma (3, 4). Of note is also a recent study analyzing the impact of PET on the intended cancer management, which involved 1,784 PET scans in MM patients and revealed that PET in MM induced a change in the intended management in 48.7% (9), entirely in line with our results as presented in this case.

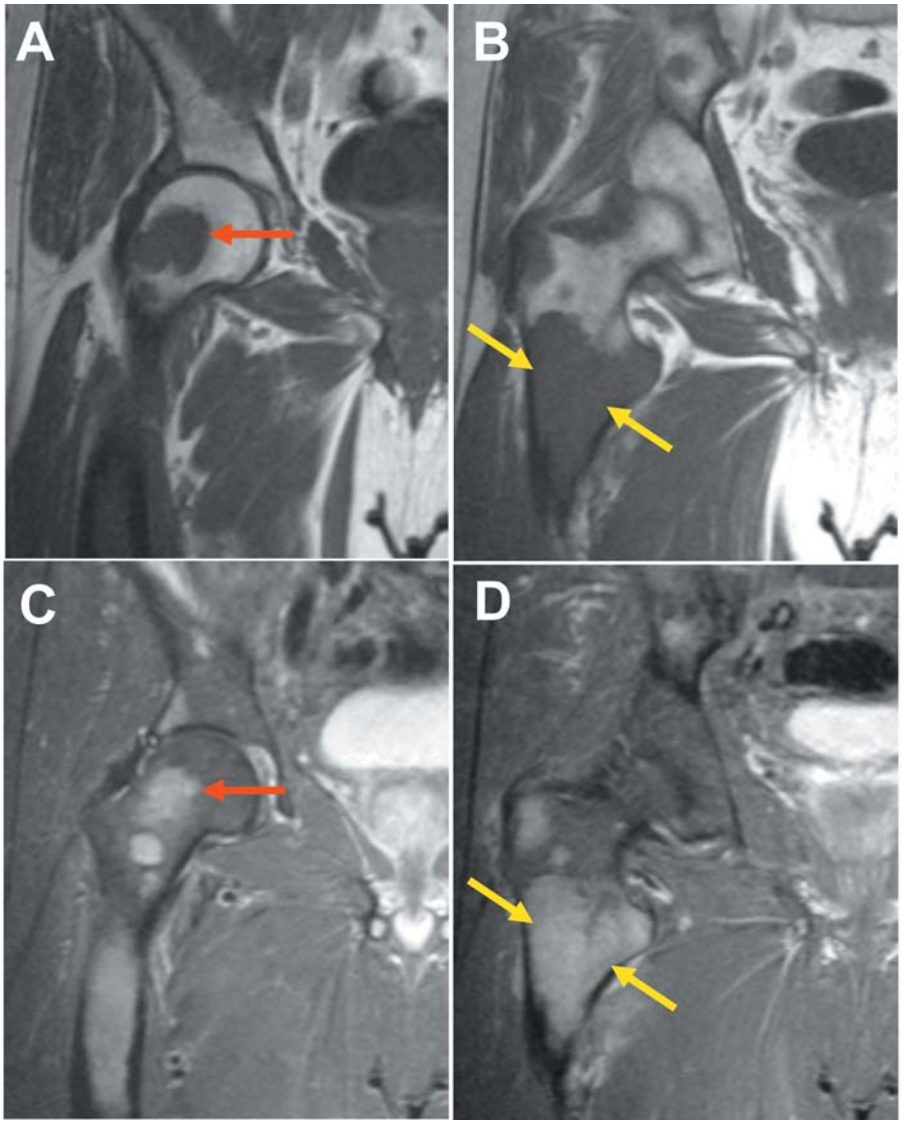

Figure 2. *Standard T1-weighted (A,B) and T2-weighted (C,D) MRI sequences showing osteolytic lesions and dense bone marrow infiltration very distinctly. Compare with plain x-ray taken 3 days later (Figure 1C).*

The inherent problem with additional imaging strategies, such as MRI and PET/CT, is of both a technical and economical nature as well as limited accessibility and facility capacity, even at well-equipped university hospitals. Their apparent benefit for the patient associated with their sensitivity needs to be weighted against the demands of the examination and cost-effectiveness which should be clarified in ongoing studies. Our case unambiguously confirms the utility and advantages of MRI and/or PET/CT in selected patients and is in line with both consensus statements and recent registry data which have indicated a potential clinical benefit with more sensitivity imaging tools, which needs to be assessed in clinical trials (8, 9).

One may critically argue that more sensitive imaging is widely performed in MM today, that most clinicians are well aware of the limitations of plain radiology in the assessment and follow-up, and most of us would seek alternative imaging methods, including MRI, in these patients. To evaluate how many MM patients indeed receive MRI or CT at initial diagnosis (ID), we analyzed all ID MM patients at our institution in 2006, 2007 and 2008: of 45, 65 and 56 newly diagnosed symptomatic MM patients, 40%, 43% and 36% received MRIs or CTs at ID, respectively (Table II). Nevertheless, these were performed in only around 40% as routine MRIs/CT, whereas in approximately 60% due to aggravating symptoms (*e.g.* bone pain). Thus, routine MRI/CT

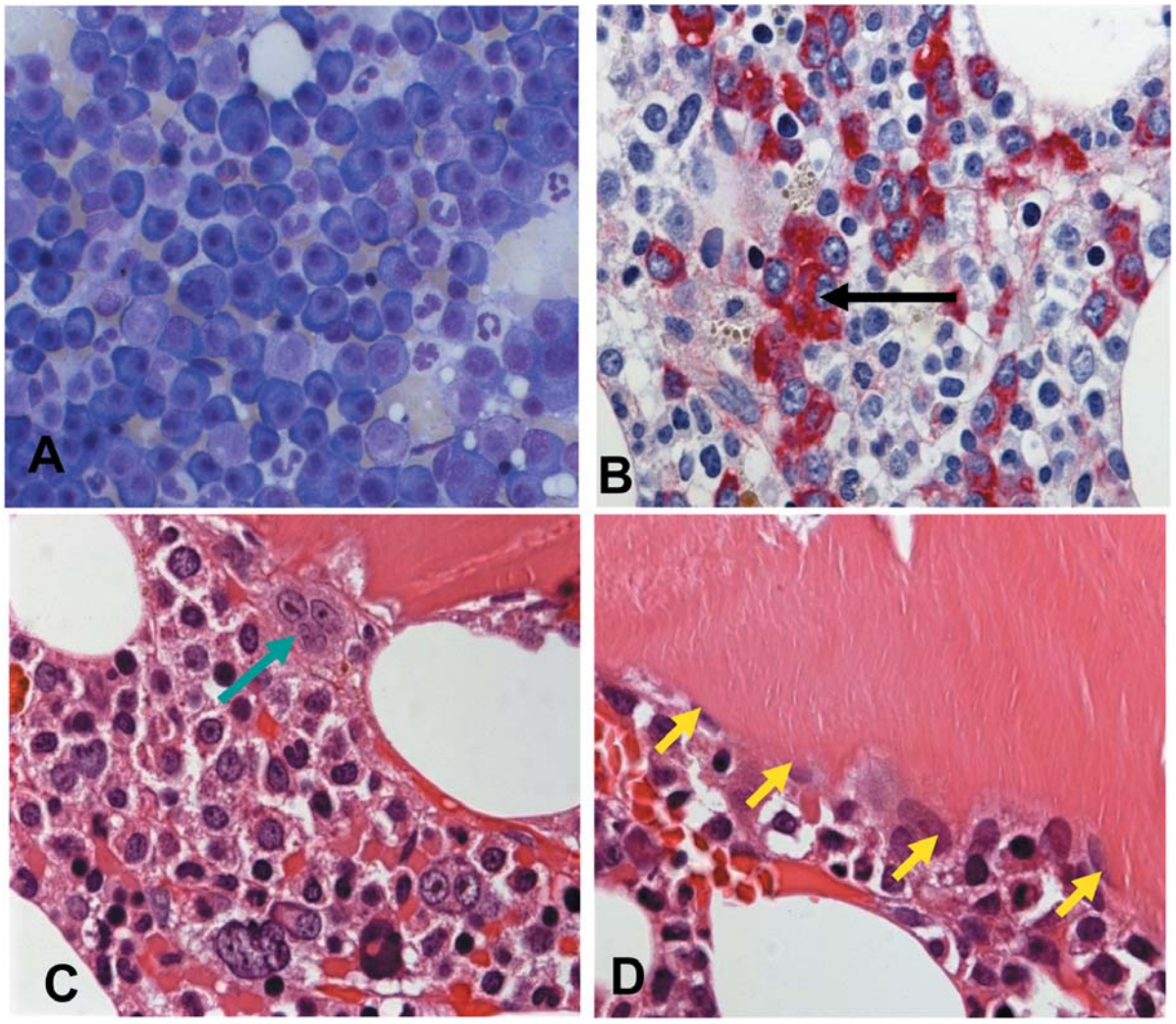

Figure 3. *Bone marrow cytology revealed densely infiltration bi-and multinucleated plasma cells (PCs) (A) which proved to be kappa-positive (B). Histopathology sections showed osteolytic features with predominant osteoclasts (C), as well as bone-infiltrating and bone-destructive plasma cells (D), the latter correlating with the aggressively osteolytic course of MM.*

Table II. *Frequency (number) of MRI and CT imaging in symptomatic MM patients (pts) at initial diagnosis (ID), University of Freiburg in 2006, 2007 and 2008.*

	2006	2007	2008
Number of MM pts with initial diagnosis in 2006-2008	45	65	56
Number of whole body MRI or CT performed at ID	18	28	20
Number of MRI	15	11	9
Number of CT	3	17	11
Number (%) of MRI/CT performed as routine screening/staging	8 (44%)	9 (32%)	8 (40%)
Number (%) of MRI/CT performed due to symptoms (bone pain)	10 (56%)	19 (68%)	12 (60%)
% of MM pts with executed MRI/CT at ID	40%	43%	35.7%
% of MM pts with routine MRI/CT	18%	14%	14.3%
% of MM pts with MRI/CT due to symptoms	22%	29%	21.4%

Symptomatic MM pts: stage II/III MM accoring to Durie & Salmon.

in newly diagnosed MM patients was performed in 14-18%, and due to symptoms in 21-29% (Table II). This illustrates that we may consider more sensitive imaging methods of importance and to be frequently used, although in daily practice these are used in <20% of MM patients for routine assessment (Table II). This also suggests that extensive bone and extramedullary disease may indeed often be missed or underestimated, as clearly demonstrated in our patient.

Therefore, we consider the presented case as an important example that calls for an earlier integration of MRI and/or PET/CT scanning in MM, especially if bone disease is substantial and/or symptoms (bone pain) recur, even if RSS remains unchanged. Whole-body (WB)-MRI is increasingly accepted for oncological staging (10). Continuous technical refinements have led to WB-MR imaging protocols, such as move during scan (MDS), which are now easy to perform with reduced scanning time (10). This may ultimately render this technique a cost-effective, sensitive, and easily reproducible tool not only for diagnosis. It may furthermore open up the possibility to integrate MRI in the initial screening and follow-up of MM patients. In the patient presented herein, the exact information from MRI induced a substantial change in the patient's prognosis (due to extramedullary MM). The time course of information and linked decision-making point towards the future significance of an intensified integration of imaging methodologies, which may become integral in the classification and disease management of MM.

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