

# The Association of Radiological Manifestations (by Both X-Ray and MRI) with the Clinical Presentation of Multiple Myeloma

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## Abstract

**Background:** Multiple myeloma (MM) is a neoplastic plasma cell disorder that arises within the bone marrow. Bone destruction is an integral part of MM. With radiological tests, about 75% of patients show punched-out lytic lesions, osteoporosis or fractures on conventional radiography. However with more sensitive tests, like computerized tomography (CT) and magnetic resonance imaging (MRI), nearly all patients show evidence of bone destruction. These more sensitive tests can be applied to define bone marrow abnormalities in MM with greater sensitivity than other imaging modalities.

**Patients and Methods:** Forty-one patients, newly diagnosed with multiple myeloma, were enrolled in this study. In addition to a clinical examination, both X-rays and spine MRI images were studied in relation to the main clinical and laboratory features like anemia, renal impairment or hypercalcemia as well as the bone marrow plasma cell degree of infiltration. The X-ray radiological abnormalities were described as normal, punched-out lytic lesions, osteoporosis or pathological fracture or any combination of these while MRI patterns were seen as normal, focal lesions or diffuse involvement.

**Results:** It appeared that the more advanced X-ray radiological features would indicate more plasma cell infiltration in the bone marrow specimen ( $p=0.047$ ) and the higher risk of renal impairment as a complication ( $p=0.05$ ) while the more diffuse pattern of MRI findings would indicate higher bone destruction and more calcium mobilization to circulation ( $p=0.05$ ).

**Conclusion:** It is clear that almost all MM patients had been referred to the hematology clinic in an advanced symptomatic stage as they had the worst manifestations of the illness (anemia and impaired renal function) as well as advanced radiological features that give no significant superiority to the MRI over the conventional X-ray screen, unlike what has been proven by other studies. A special MRI protocol for MM patients may be required to yield better results in assessing the degree of plasma cell infiltration in bone marrow; allowing it to be applied in follow-ups for those patients.

**Keywords:** Multiple myeloma, plasma cell disease, imaging tests in multiple myeloma, MRI, X-ray, prognosis.

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## **Background**

Multiple myeloma (MM) is a neoplastic plasma cell disorder. It forms 1% of all types of cancers. This malignant disease arises in the bone marrow and results in anemia, immunoparesis and skeletal destruction in addition to abnormal paraprotein production as monoclonal immunoglobulin in serum and/or urine. The median age at diagnosis is 70 years.<sup>1,2</sup>

Bone destruction is an integral part of MM and is seen in at least 70% of patients. When more sensitive imaging tests are used, nearly all patients show evidence of bone destruction and its complications.<sup>3</sup> Bone disease in MM most frequently involves the spine as well as the extremities. It is a major source of morbidity and presents as bone pain in around two-thirds of affected patients.

On conventional radiographic examination, around 75% of patients may have punched-out lytic lesions, osteoporosis or pathological fractures. The vertebrae, skull, ribs, sternum and proximal bones are most frequently affected.<sup>4</sup> A small subset may have de novo osteosclerotic lesions, which may also occur after therapy as a marker of healing.<sup>5</sup>

Computerized tomography (CT) and magnetic resonance imaging (MRI) are more sensitive than conventional radiography and they may reveal specific lesions in 90% of stage 1 MM patients.<sup>6</sup> MRI is a non-invasive technique which can sample a large volume of bone marrow and can be applied to define bone marrow abnormalities in MM with greater sensitivity than other imaging modalities.<sup>7</sup> Among asymptomatic MM patients who have normal radiography, 50% may demonstrate abnormal MRIs.<sup>8</sup> Thus, the latter may be useful to distinguish patients at high risk or low risk for progression.<sup>9</sup> The three MRI patterns in MM are described as normal, focal lesions or diffuse inhomogeneous (variegated) infiltrations,<sup>10</sup> and they may provide value as predictors in newly diagnosed patients or those who have received chemotherapy.<sup>10</sup>

Many centers today are using sophisticated tests to assess the disease stage; like FDG-PET/CT (fluorodeoxy-D-glucose positron emission technique). These may be able to detect more lytic lesions, which are out of the field of view of the MRI.<sup>11,12</sup>

## **Objectives**

Assessment of the association between clinical presentation and radiological manifestation in multiple myeloma patients.

## **Patients and Methods**

Forty-one patients, newly diagnosed with multiple myeloma, were enrolled in this study, performed between Jan 2007 and April 2010 at Al Kadhimiya teaching hospital in Baghdad, Iraq. For each patient, a full medical history and examination were performed. The diagnosis was settled upon with the aid of clinical presentation as well as laboratory investigations including CBC (complete blood count), BM (bone marrow) aspiration and biopsy, SPE (serum protein electrophoresis) and urine screening for light chain excretion.

Conventional skeletal surveys (skull, pelvis and dorsolumbar spine X-rays) were conducted. Baseline MRIs for thoracic and lumbar spines were taken for each patient before any treatment was given.

The X-ray radiological abnormalities were described as normal, punched-out lytic lesion, osteoporosis, pathological fracture or any combination of these.

On MRI features, patterns were described as one of the following:

1. Normal: reported in cases with no evidence of abnormalities.
2. Focal pattern: consisting of localized area of abnormal marrow that appears on:
  - T1-weighted images as darker than yellow marrow and red marrow
  - T2-weighted images as brighter than both yellow and red marrow.

- Enhanced T1-weighted images as enhanced lesions to variable degrees after intravenous contrast
- 3. Diffuse: An MRI pattern of abnormal marrow where the normal marrow is completely replaced by an abnormal process and the intervertebral disks will appear brighter than, or iso-intense with, the diseased marrow appearing on:
  - T1-weighted images, as diffuse decrement in the signal intensity of the marrow.
  - T2-weighted images, as a variable increment in signal intensity of the abnormal marrow.
  - Enhanced T1-weighted images, after intravenous contrast, the intervertebral disks appear darker than the enhanced spine.

The review of the initial presenting laboratory abnormalities were also assessed, hemoglobin level, serum creatinine and serum calcium, for the purpose of assessment of disease severity.

The glomerular filtration rate (GFR) was not calculated as the objective was to assess early short-term complications rather than long-term ones.

International Staging System (ISS) scoring couldn't be applied as the serum B2 microglobulin level wasn't available. SPSS v.10 was used for statistical assessment of this study.

## Results

### *Patients' Characteristics*

Of the forty-one patients included in this study, 22 (53.7%) were female, while the rest were male (46.3%). The patients' mean age was 61.8±10.49 years. (Table 1)

**Table (1): Patient Characteristics.**

<u>Character</u>	<u>Range</u>	<u>Mean +SD</u>
Age (year)	36-81	61.8±10.49
Hb (g/dl)	4-12	7.69±1.91
Plasma cell in BM (%)	40-98	79.95±15.47
Serum creatinine (mg/dl)	0.9-3.0	1.79±0.60
Serum calcium (mmol/l)	1.6-3.0	2.36±0.33

### **Radiological Features**

Gender difference has no statistical significance with radiological findings in either imaging group: X-ray and MRI (p= 0.39, p=0.12 respectively). (Table 2)

### **Application of X-ray Findings with the Patients' Clinical Manifestations of Multiple Myeloma**

It appears that the more advanced X-ray radiological features indicate greater plasma cell infiltration percentages in the bone marrow specimen (p=0.047) and the higher risk for development of renal impairment as an early short-term complication (p=0.05) at the time of clinical presentation, unlike other parameters, such as the hemoglobin level (p=0.24) or the serum calcium level (p=0.215). (Table 3)

### **Application of MRI Findings with Patient Clinical Manifestations of Multiple Myeloma**

The more diffuse pattern of the MRI findings indicated higher bone destruction and more calcium mobilization to circulation (p=0.05), but no clear relationship to the other parameters. (Table 4)

### **MRI and X-ray**

There was no significant association between the findings of the MRI and the X-ray (p=0.07). (Table 5)

**Table (2): Radiological Features.**

Conventional X-ray Features			MRI Pattern		
<u>Pattern</u>	<u>No.</u>	<u>%</u>	<u>Pattern</u>	<u>No.</u>	<u>%</u>
Normal	9/41	22	Normal	5/41	12
Punched-out lytic lesions	11/41	27			
Osteoporosis	10/41	24	Focal	10/41	24
Combination	11/41	27	Diffuse	26/41	63

**Table (3): The Association Between X-Ray Radiological Features and Multiple Myeloma Clinical Manifestations.**

<i>X ray features</i>	<i>Hemoglobin (mean±SD) g/dl</i>	<i>Plasma cell in bone marrow (mean±SD)%</i>	<i>Serum creatinine (mean±SD) g/dl</i>	<i>Serum calcium (mean ±SD)mmol/l</i>
Normal	7.9±1.67	74.00±20.38	2.01±0.72	2.27±0.37
Lytic lesion	8.3±2.83	73.67±16.17	1.47±0.38	2.30±0.34
Osteoporosis	7.98±1.35	89.1±7.47	1.70±0.66	2.29±0.34
Combination	6.6±0.96	82.81±12.05	2.00±0.55	2.56±0.23
<i>P value</i>	0.24	0.047*	0.05*	0.215

**Table (4): Relationship between MRI Patterns and Multiple Myeloma Clinical Manifestations.**

<i>MRI pattern</i>	<i>Hemoglobin (mean±SD)g/dl</i>	<i>Plasma cell in bone marrow (mean±SD) %</i>	<i>Serum creatinine (mean±SD) g/dl</i>	<i>Serum calcium (mean ±SD) mmol/l</i>
Normal	8.6±1.49	74.4±19.34	1.5±0.56	2.14±0.11
Focal	7.73±1.73	79.8±17.48	1.84±0.58	2.34±0.37
Diffuse	7.50±2.04	81.07±19.34	1.82±0.63	2.41±0.34
<i>P value</i>	0.88	0.46	0.72	0.05*

**Table (5): Relationship Between X-ray Features and MRI Patterns.**

<i>MRI Patterns</i>	<i>Normal</i>	<i>X ray features</i>			<i>Total</i>	
		<i>Normal</i>	<i>Lytic lesions</i>	<i>Osteoporosis</i>		<i>Combinations</i>
<i>Normal</i>		3	0	2	0	5
<i>Focal</i>		2	5	2	1	10
<i>Diffuse</i>		4	6	6	10	26
<i>Total</i>		9	11	10	11	41

*P=0.07*

## Discussion

Throughout this study, it is clear that almost all multiple myeloma patients had been referred to the hematology clinic in an advanced symptomatic stage as they had the worst manifestations of the illness (anemia and impaired renal function) as well as advanced radiological features.

Surprisingly, this study shows no significant superiority of MRI over conventional X-ray imaging ( $p=0.07$ ). This is in contrast to most

studies which prove the MRI's higher sensitivity over X-ray findings.<sup>7, 10</sup> The explanation may be due to the small patient sample as well as the advanced clinical presentation of their illness at the time of study.

It has been shown that early short-term complications like renal impairment can be detected by measuring serum creatinine at the time of presentation. This may draw attention to the reversible causes (like dehydration, drug adverse effects, etc.) and save patients from a more drastic outcome. Considering that high

serum creatinine has been reported also in those presenting with normal X-rays (9 patients), it is still useful to give the statistical significance in this small sample of patients although it may be imprecise due to the lack of assessment of glomerular filtration rate.

The association between X-ray features and high serum creatinine may not only be explained on the basis of MM complications; it may be secondary to bone mineral abnormalities that complicate any case of chronic renal failure. Those cases weren't identified in this study since MM is one of the diseases that may maintain normal size kidneys despite a chronic renal failure state.

Similarly, detection of plasma cell infiltration in bone marrow has been associated with more advanced X-ray features unlike the reports of MRI manifestations. This may be understood if it is known that there is no special MRI protocol to study the marrow at the time of examination (they had been requested by either the neurosurgeon or rheumatologist prior to patients' referral to the hematologist) as well as the fact that only the spine was studied.

An MRI protocol for a MM patient consists of T1 weighted images, fast spin echo T2 weighted images with fat saturation and contrast enhanced T1 weighted images.<sup>14, 15</sup> With the aid of these techniques, the MRI is considered as a qualitative measure for the degree of marrow infiltration, similar to a bone marrow biopsy, according to the degree of hyperintensity.<sup>10, 13</sup> The T1 weighted image is the most sensitive test in depicting bone marrow abnormalities<sup>14, 15</sup> and is useful in assessing the relationship between MRI pattern and bone marrow plasmacytoma.<sup>10, 13, 14</sup> In diffuse MRI patterns, the change in signal intensity may depend on the percentage of plasma cells in the bone marrow. However, it may give false negative study if the infiltration is insufficient.<sup>14</sup>

MRI reassessment after treatment is encouraged by Mouloupoulos et al. as a confirmation of resolution of primary marrow abnormality or

persistent abnormality but, without enhancement, it may be not considered as complete assessment.<sup>10</sup> However, given the expense of an MRI, it cannot be recommended for routine clinical follow-ups.

In another study, MRI findings are considered to be the best independent prognosticators for survival, as patients with diffuse patterns had more bone marrow plasma cells as well as high serum calcium, high B2 microglobulin and low hemoglobin concentrations.<sup>13, 14</sup> This is partially verified in this study.

Abnormal MRI patterns may occur in 30-40% of patients in early asymptomatic stage MM and may indicate the increased likelihood of disease progression within subsequent years.<sup>9, 16</sup>

The high serum calcium level that correlated more with diffuse MRI patterns (P=0.05) is a good indicator of heavy skeletal damage that may mobilize calcium from the bone minerals to circulation. The conventional X-ray did not show this association since it is less sensitive for screening the bone density.

The hemoglobin level did not show any association with any imaging findings. This can be simply accepted because of the potential for the effects of abuse, the early decision for a blood transfusion or the habitual use of tonics used commonly by most practitioners.

In conclusion, MRI is very useful for assessing MM severity and it may also be useful to assess the response to treatment as well as the prognosis, due to its capacity to determine the marrow infiltration. It is recommended that it be determined whether different MRI pattern presentation may imply different prognostic capacity or necessitate different protocol therapy.

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## علاقة مظاهر الأشعة التشخيصية بواسطة الأشعة السينية وتصوير الرنين المغناطيسي مع العلامات السريرية لمرض الورم النقوي المتعدد

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### الملخص

**الخلفية:** الورم النقوي المتعدد هو ورم خلايا البلازمويات الموجودة في نخاع العظم والمتسبب غالباً في الدمار العظمي الذي هو من العلامات الأساسية للمرض. مظاهر المرض المقرونة بالفحوصات الأشعة التشخيصية والمثبتة عند 75 % من المرضى هي على شكل ثقب جروح أو وهن العظام أو كسور بحسب الأشعة السينية، لكن ما يظهر بالإختبارات الأكثر حساسية، هو وجود أدلة الدمار العظمي في كل المرضى تقريباً مثل جهاز الفحص المقطعي الالكتروني (سي تي) وتصوير الرنين المغناطيسي.

**المرضى والطرق:** تم جمع واحد وأربعين مريضاً مصابين بالورم النقوي المتعدد حديثاً في هذه الدراسة. وبعد إجراء الفحص السريري لكل منهم، أجري تصوير الأشعة السينية وتصوير الرنين المغناطيسي العمود الفقري. تم إجراء الدراسة لمعرفة العلاقة بين بعض العلامات السريرية أو المختبرية مثل ( فقر الدم، ضعف كلوي أو اختلال الكالسيوم بالإضافة إلى درجة انتشار الخلايا البلازموية في نخاع العظم. شذوذ تصوير الأشعة السينية وصف على نحو طبيعي، ثقب جروح، وهن عظم أو كسر مرضي أو أية مجموعة مشتركة لأي منهم بينما أنماط التصوير بالرنين المغناطيسي كانت على نحو طبيعي، جروح بؤرية أو تدخل مستفيض.

**النتائج:** أظهرت نتائج البحث أن المظاهر المتقدمة للمرض من خلال الأشعة السينية تشير إلى انتشار الخلايا البلازموية في نخاع العظم (  $p = 0.047$ ) ونسبة خطر أعلى للإصابة بالضعف الكلوي كمضاعفات ( $p = 0.05$ ) بينما النمط الأكثر إستفاضة بالتصوير بالرنين المغناطيسي يشير إلى امكانية الدمار العظمي الأعلى وتعبئة الكالسيوم الأكثر إلى التوزيع في الدم ( $p = 0.05$ ).

**المناقشة والاستنتاج:** من الواضح جداً أن كل المرضى الداخليين في الدراسة هم في المرحلة العرضية المتقدمة حيث أن هناك الكثير من التعقيد والمضاعفات عند استقبال الحالات، هذا بالإضافة إلى كونهم قد سجلوا مظاهر إشعاعية تشخيصية من دون أي تفوق للمزايا الظاهرة بالتصوير بالرنين المغناطيسي بالمقارنة مع المظاهر المسجلة على شاشة الأشعة السينية التقليدية على خلاف ما تم تثبيته من قبل الآخرين. إن استخدام نظام التصوير بالرنين المغناطيسي متخصص لمرضى الورم النقوي المتعدد قد يكون أكثر فاعلية ويساعد في تقييم درجة تسرب الخلايا البلازموية في نخاع العظم ولذا هو قد يطبق في متابعة تطور أولئك المرضى.

**الكلمات الدالة:** مرض ورم نقوي متعدد، ورم البلازمويات، التصوير الشعاعي السيني، التصوير بالرنين المغناطيسي، مضاعفات الورم النقوي المتعدد.