Multiple Myeloma: Clinical Review and Diagnostic Imaging

Multiple myeloma (MM) is a neoplasm of terminally differentiated plasma cells. It accounts for approximately 1% of all malignant diseases and represents about 10% of hematologic malignancies. The annual incidence of newly diagnosed cases in the United States is three to four per 100,000 population per year, with an estimated 14,000 new cases each year. The median age at diagnosis is 65 years, and about 3% of patients are younger than 40 years (1). The disease has a higher incidence in men and African Americans.

The cause of MM is unknown. Radiation exposure increases the risk, as evidenced by a higher than expected rate of disease in atomic bomb survivors, radiation workers, and postirradiated patients with ankylosing spondylitis. The origin of the malignant plasma cell remains a mystery. Data from cloning and gene-sequencing studies strongly imply that the malignant clone in MM arises from a late cell in B-cell development (2,3).

**CLINICAL PRESENTATION**

The clinical findings vary from totally asymptomatic in patients whose disease is discovered incidentally to life-threatening symptoms. The common clinical presentations are fatigue and bone pain (back or ribs) with or without associated fractures or infection. In 15%–30% of patients (4), the finding at presentation is hypercalcemia with concomitant renal insufficiency caused by precipitation of monoclonal light chains in the collecting tubules (5). Ten percent of patients present with other symptoms, including hyperviscosity syndrome, compression of the spinal cord (Fig 1), radicular pain, soft-tissue deposits, or bleeding problems. In patients who are asymptomatic, the disease is incidentally discovered because of laboratory findings of anemia or hyperproteinemia.

The hallmark of MM is the detection in blood and/ or urine of a monoclonal protein, M protein, produced by the abnormal plasma cells. Serum protein electrophoresis reveals a
localized band in the globulin part of the α (immunoglobulin [Ig] A) or γ (IgG) region in 80% of patients. The remaining 20% of patients will have either hypogammaglobulinemia or a normal-appearance pattern (nonsecretory type). By using the more sensitive techniques of immunofixation and immunoelectrophoresis, M protein (in serum or/and urine) will be detected in 99% of patients (6). The IgG isotype is seen in 60% of MM patients; the IgA isotype, in 25%; the IgD isotype, in 1%; the IgM isotype in 1%; and light chain disease, in 20%.

Once the diagnosis is suspected, a radiographic skeletal survey and bone marrow aspiration and biopsy are performed. Samples are sent for plasma cell labeling index and cytotgenetic analyses. Minimal criteria for establishment of a diagnosis of MM should be the detection of at least 10% abnormal plasma cells in a random bone marrow biopsy specimen and M protein in either the serum (usually >3 g/dL) and/or urine (usually >1 g/24-hour collection). Osteolytic lesions on a skeletal survey may be found (7). In most patients, the diagnosis of MM is established without difficulty.

**CLINICAL STAGING AND PROGNOSIS**

In patients known to have MM, clinical stage is based on the Durie-Salmon system (8) (Table 1). Staging criteria are simple and help estimate suspected tumor burden. This system is based on a combination of clinical factors: amount of M protein, serum hemoglobin level, serum calcium level, number of lytic bone lesions on a skeletal radiographic survey, and renal function. The staging system is used as a predictor of patient outcome and is currently used as a standard for ongoing clinical trials.

Prognosis for the disease is highly variable, with survival ranging from a few months to more than 10 years (9). In recent years, advances in the treatment of the disease have resulted in substantially improved clinical outcomes, with improved overall survival and better response to chemotherapeutic regimens, particularly high-dose therapy. Other prognostic factors have been developed that help better identify the subgroups of patients with different outcomes and tailor treatment intensity to disease risk.

Serum β2-M level is one of the most important prognostic factors in MM. The level is a measure of tumor burden and renal function (10). C-reactive protein level is another important predictive factor. C-reactive protein is a surrogate marker of interleukin 6, which is an osteoclast-activating factor. The combination of high levels of C-reactive protein and β2-M indicates a poor prognosis in MM patients who were treated with conventional chemotherapy (11). The plasma cell labeling index reflects the proliferative capacity of plasma cells. The index typically increases during disease progression (12). The median survival of patients with a low plasma cell labeling index and low β2-M level who are treated with conventional chemotherapy is 71 months, compared with 17 months when both parameters are elevated (13).

Elevated lactate dehydrogenase levels are predictive of short survival, as they are frequently associated with plasmablastic morphology, extramedullary sites of disease, and adverse-risk cytogenetic abnormalities (14). The presence of cytogenetic abnormalities has recently emerged as the most important prognostic factor in MM. Abnormal karyotypes are observed in 30%–50% of MM patients (15)—more frequently in patients with relapse (35%–63%) than in those with newly diagnosed disease (20%–30%). Karyotypic abnormalities are complex, involving more than three chromosomes in 80% of the patients (16). Multiple trisomies and trans-
Before a discussion of imaging findings in MM, it is important to understand myeloma bone disease. The effects of abnormal plasma cells on bone lead to severe bone pain and skeletal fractures, especially spinal compression fractures. Histologic studies of bone have revealed excessive bone resorption in the vicinity of the myeloma cells, with severe inhibition of bone formation (18). Once myeloma cells invade the bone marrow, they adhere to the stromal cells and induce secretion of osteoclast-activating factors, including interleukins 6 and 1β and tumor necrosis factor-β. These factors prompt the stromal cells and osteoblasts to secrete tumor necrosis factor-related induced cytokine, or TRANCE, a member of the tumor necrosis factor family (19), which induces differentiation and maturation of osteoclast progenitors (20). The activity of TRANCE can be blocked by osteoprotergerin. The delicate balance between TRANCE and osteoprotergerin, which normally regulates the osteoclastic activity in healthy individuals, is totally disrupted in patients with MM. This disruption is due to overproduction of TRANCE and inactivation of osteoprotergerin by elevated amounts of syndecan-1, a molecule actively shed from the plasma cell surface. Furthermore, unchecked osteoclastic activity promotes the production and release from stromal cells of various cytokines, which lead, directly or indirectly, to further MM clone proliferation. A vicious cycle, with bone destruction “feeding” tumor growth and MM cells promoting bone destruction, is therefore set in motion (21). This set of factors leads to the common findings in MM: severe osteopenia and multiple spinal compression fractures.

This vicious cycle can be broken by the use of bisphosphonates. These agents (used in conjunction with cytotoxic chemotherapy) have been found to be superior to chemotherapy alone in decreasing skeletal-related events in MM patients, such as need for radiation therapy, pathologic fractures, and bone pain (22). Besides their skeletal effects (achieved through direct osteoclast inhibition), bisphosphonates may have an antmyeloma effect (23), and their use may lead to prolonged survival in myeloma patients (24).

**IMAGING STUDIES**

The role of imaging in the work-up of patients with MM consists of studies that allow recognition of the effects of myeloma cells on the skeletal system. In the past, these studies included radiographic skeletal surveys, computed tomography (CT), and nuclear medicine bone scanning (7). Recently, MR imaging of bone marrow has allowed a direct look at the actual tumor burden within the bone marrow (25–30). Direct visualization of marrow disease allows assessment of the extent of disease in newly diagnosed cases and of the effects of therapy. More recently, positron emission tomography (PET) with fluorodeoxyglucose (FDG) has been used to study relapsing patients in whom recurrent disease is not easily detectable with routine imaging. PET, in this instance, has been found to aid in detection of unsuspected sites of medul- lar and extramedullary disease (31).

**TABLE 1**

**Durie-Salmon Staging System for MM**

<table>
<thead>
<tr>
<th>Stage and Criteria</th>
<th>Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>I: Low tumor burden†</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin level</td>
<td>&gt;10 g/dL (100 g/L)</td>
</tr>
<tr>
<td>Serum calcium level</td>
<td>&lt;12 mg/dL (3 mmol/L)</td>
</tr>
<tr>
<td>Radiograph</td>
<td>No bone destruction, or solitary plasmacytoma</td>
</tr>
<tr>
<td>Low paraprotein level</td>
<td></td>
</tr>
<tr>
<td>Serum IgG</td>
<td>&lt;5 g/dL (0.05 g/L)</td>
</tr>
<tr>
<td>Serum IgA</td>
<td>&lt;3 g/dL (0.03 g/L)</td>
</tr>
<tr>
<td>Urine light chain</td>
<td>&lt;4 g/24 h</td>
</tr>
<tr>
<td>II: Intermediate tumor burden</td>
<td></td>
</tr>
<tr>
<td>All criteria</td>
<td>Between values for stage I and values for stage III</td>
</tr>
<tr>
<td>III: High tumor burden‡</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin level</td>
<td>&lt;8.5 g/dL (85 g/L)</td>
</tr>
<tr>
<td>Serum calcium level</td>
<td>&gt;12 mg/dL (3 mmol/L)</td>
</tr>
<tr>
<td>Radiograph</td>
<td>More than two advanced lytic lesions</td>
</tr>
<tr>
<td>High paraprotein level</td>
<td></td>
</tr>
<tr>
<td>Serum IgG</td>
<td>&gt;7 g/dL (0.07 g/L)</td>
</tr>
<tr>
<td>Serum IgA</td>
<td>&gt;5 g/dL (0.05 g/L)</td>
</tr>
<tr>
<td>Urine light chain</td>
<td>&gt;12 g/24 h</td>
</tr>
<tr>
<td>Associated renal involve ment</td>
<td></td>
</tr>
<tr>
<td>A: serum creatinine level</td>
<td>&lt;2 mg/dL (177 μmol/L)</td>
</tr>
<tr>
<td>B: serum creatinine level</td>
<td>&gt;2 mg/dL</td>
</tr>
</tbody>
</table>

* Value in parentheses is in SI unit.
† All criteria must be satisfied.
‡ Any criterion must be satisfied.

**SKELETAL RADIOGRAPHY AND CT**

Skeletal radiography continues to be the primary diagnostic study to aid in detection of destructive bone changes in MM. Estimates suggest that approximately 50% of bone destruction must occur before there is radiographic demonstration of the abnormality and that 75% of patients with MM will have positive radiographic findings (28). Four distinct forms of involvement have been described: the solitary lesion (plasmacytoma), diffuse skeletal involvement (myelomatosis), diffuse skeletal osteopenia, and sclerosing myeloma (32).

Plasmacytomas typically are lytic lesions that primarily affect the spine, pelvis, skull, ribs, sternum, and proximal appendages (28). The skeletal radiographic survey continues to have an important role in the Durie-Salmon clinical staging criteria for newly diagnosed MM. The presence of two clearly defined lytic lesions indicates high tumor burden and stage III disease (8). In addition, the skeletal survey is used to judge progression of disease and has a complementary role to MR imaging in following the course of disease in patients with MM (33). Diffuse myelomatosis classically manifests as osteolytic lesions with discrete margins and uniform size. These lesions are often subcortical and elliptic and may coalesce into large segments of destruction. Diffuse skeletal osteopenia without well-defined lytic lesions predominantly involves the spine. Multiple compression fractures may be seen with this condition. Bone sclerotic lesions are seen in MM and are associated with the polynuropathy, organomegaly, endocrinopa-
thy, monoclonal gammopathy, and skin changes, or POEMS, syndrome (34,35).

CT is a sensitive tool for detection of the bone-destructive effects in MM (Fig 2). CT findings consist of punched-out lytic lesions, expansile lesions with soft-tissue masses, diffuse osteopenia, fractures, and, rarely, osteosclerosis (28,36) (Fig 3). Recently, Mahnken et al (36) compared multi–detector row CT with conventional radiography and MR imaging in 18 patients with newly diagnosed MM. Multi–detector row CT was superior to conventional radiography for defining lytic lesions and, in combination with MR imaging, aided in staging the extent of disease. Multi–detector row CT allowed a better evaluation of areas at risk for fracture than did MR imaging. Our experience with the role of CT in MM has been with its adjunctive role in defining possible lytic or sclerotic lesions and in guidance for spinal and pelvic biopsy of MR imaging–defined focal lesions (37).

NUCLEAR MEDICINE STUDIES

Utilization of the various nuclear medicine radiopharmaceuticals in MM relate to either a direct association with tumor biology (ie, imaging of tumor cells) or an indirect effect (eg, imaging of compression fractures, dystrophic calcifications).

MM is primarily an osteolytic neoplasm. However, detection of bone involvement with the usual technetium 99m (99mTc)–based bone scanning agents relies on an osteoblastic response of the skeletal system for uptake. Bone scans obtained with 99mTc have therefore resulted in underappreciation of the extent of disease (34,35, 38–40). In a report (34) comparing the skeletal radiographic survey with bone scans, uptake of the radioisotope in radioisotope in radioisotope in radioisotope in radioisotope in radioisotope in radioisotope in radioisotope in radioisotope in radioisotope in radioisotope in radioisotope in radioisotope in radioisotope in radioisotope in radioisotope in radioisotope in radioisotope in radioisotope in radioisotope in radioisotope in radioisotope in radioisotope in radioisotope in radioisotope in radioisotope in radioisotope in radioisotope in radioisotope in radioisotope in radioisotope in radioisotope in radioisotope in radioisotope in radioisotope in radioisotope in radioisotope in radioisotope in radioisotope in radioisotope in radioisotope in radioisotope in radioisotope in radioisotope in radioisotope in radioisotope in radioisotope in radioisotope in radioisotope in radioisotope in radioisotope in radioisotope in radioisotope in radioisotope in radioisotope in radioisotope in radioisotope in radioisotope in radioisotope in radioisotope in radioisotope in radioisotope in radioisotope in radioisotope in radioisotope

67Ga citrate localizes in areas of active tumor either through primary localization within the tumor or through the secondary “inflammatory response” induced by the tumor. This inflammatory response is evidenced by the associated presence of mononuclear cell and lymphocytic infiltrates observed with the plasma cells. Whether these mechanisms act singly or in combination remains unknown (43–46). 67Ga is not likely to be used in tumor detection in MM owing to its expense, lack of advantage over sestamibi or PET imaging, and possible need for multiday scanning. In instances where infection is suspected in MM patients, 67Ga citrate may be used and uptake by the tumor may be observed.

201Tl chloride has also been used in the detection of MM. The mechanism of uptake is either increased metabolic demands of the tumor or secondary inflammatory response induced in the marrow (47). A recent study comparing 201Tl and 99mTc bone scans in MM found 201Tl to be promising in detection of disease owing to its complementary detection rates (48). The role of this agent in MM is, however, currently supplanted by 99mTc sestamibi, which shows similar localization on images of higher quality and lower cost. 99mTc sestamibi is thought to accumulate preferentially in malignant cells, owing to a higher transmembrane electric potential that results from a higher metabolic rate in MM cells (49–52). The primary site of localization is in the mitochondria (52,53). Pace et al (50) classified the activity patterns of 99mTc sestamibi as focal, diffuse, a combination of focal and diffuse, or normal in 39 patients with MM. Activity was correlated with active disease, and nor-
mal scans were related to remission. Unfortunately, the value of follow-up studies is limited because of the known development of multidrug resistance by myeloma cells, which causes blockade of the accumulation of the sestamibi (54–57).

Fluorine 18 FDG PET has been reported in MM (58,59). In a series of 43 patients with MM and solitary plasmacytoma, Shirrmeister et al (31) reported a case of combined use of 99mTc sestamibi and FDG PET, where the former seemed to correlate better with overall extent of disease and the latter with areas of active disease.

One final use of nuclear medicine in MM is in the evaluation of patients for the treatment of painful bone metastases. Isotopes such as strontium 89 (89Sr) have been used to palliate the pain in MM (60). Because response is dependent on osteoblastic activity, a purely osteolytic process might not be effectively treated. A routine bone scan can help document the presence of osteoblastic response in these patients and is therefore helpful to predict response to 89Sr treatment.

**MR IMAGING**

MR imaging findings in MM closely reflect the broad spectrum of pathologic tumoral spread (25–30). The distribution of malignant plasma cells in MM includes sites that show normal areas of active hematopoiesis in adults. These are in the bone marrow of the axial skeleton. The combination of the diagnostic accuracy afforded by current MR units and the extensive coverage by phased-array spine coils allow the acquisition of survey studies of long segments of the axial skeleton within a reasonable time period. MR images can then be used to determine the exact location, size, and local compressive effects of the focal plasmacytomas and possible associated fractures. MR images can help precisely define radiation therapy ports used in the primary treatment of patients with solitary bone plasmacytoma (61). Posttreatment MR images help define response to treatment (62–64). An additional use of MR imaging is the delineation of the effects and complications of the highly involved therapeutic protocols, to help explain whether observed clinical findings are the result of complications of the disease or of a failure to respond to therapy.

**MR Imaging Parameters**

The type of MR sequence applied greatly affects the MR image. Multiple sequences have been proposed for use in identifying focal or diffuse disease of the bone marrow. These sequences include spin-echo (T1-weighted and T2-weighted),...
gradient-echo (T2*-weighted), STIR, and contrast material–enhanced spin-echo (with and without fat suppression) sequences (26,29,65–67).

T1-weighted spin-echo images generally depict a focal plasmacytoma as a hypointense area within a generally hyperintense marrow background. On the other hand, diffuse involvement is identified as generalized hypointensity of the overall marrow, compared with the intensity of the disk interspace or adjacent skeletal muscles. On T2-weighted spin-echo, gradient-echo, and STIR images, focal lesions are hyperintense relative to the hypointense marrow background. Diffuse involvement is identified as a generalized hyperintensity of the marrow background relative to the intensity of skeletal muscles. With these sequences, we believe that inclusion of a fat-suppression technique (in our experience, STIR imaging) is important, as it allows better assessment of marrow involvement (diffuse, focal, speckled) and characterization of involvement (uniform or homogeneous, nonuniform or inhomogeneous) (65–68). Contrast-enhanced studies with fat suppression can supplement these other studies with demonstration of enhancement in focal or diffuse disease.

At initial evaluation and follow-up in MM patients, we obtain survey MR images of the entire axial skeleton. These consist of T1-weighted spin-echo and STIR spin-echo sequences (sagittal projection of
spine and coronal projection of pelvis). These studies are complementary in the analysis and detection of focal and diffuse disease in MM (65–68). Gadolinium-enhanced fat-suppressed T1-weighted images are added to studies of the thoracic and lumbar spine. This allows better differentiation of smaller focal lesions and characterization of diffuse disease. Transverse T1-and/or T2-weighted images are obtained to characterize the effects of focal expansile lesions. MR imaging of the brain is performed to examine diploic involvement of the calvarium and skull base (Fig 5). This is accomplished with sagittal T1-weighted and coronal and transverse gadolinium-enhanced fat-suppressed T1-weighted sequences.

MR Imaging of Normal Marrow

In MR imaging evaluation of the marrow, the patient’s age must be taken into consideration. In the young patient, most of the marrow in both the axial and appendicular skeletons is cellular, primarily inhabited by hematopoietic cells (red marrow). In adolescence, the red marrow of the appendicular skeleton changes to yellow marrow, with change occurring initially in the diaphysis and epiphyses and later in the metaphyses. By the age of 20 years, the appendicular skeleton is mostly made of fatty elements, while the axial skeleton—the spine, pelvis, ribs, skull, and proximal metaphyses of the femur and humerus—is largely hematopoietic (69). In the 4th decade of life, the axial skeleton changes in cellular makeup to fatty marrow; by the 6th decade, the marrow is mainly fatty. On T1-weighted images, fatty marrow is hypointense and cellular marrow is hypointense, relative to the intensity of skeletal muscles. Ricci et al (70) described four normal marrow patterns in various age groups (Table 2). In the age population where MM is most often found, one should be cautious in identifying diffuse nonuniform or bandlike areas of hypointensity on T1-weighted images as abnormal, because these findings can be normal in this age group.

MR Imaging of MM

In MM, localization of tumor spread by using MR imaging closely mimics the findings in patients with spinal marrow metastasis. In general, abnormalities are identified as hypointensities on T1-weighted images, hyperintensities on STIR images, and enhancement on gadolinium-enhanced images. These imaging features are not pathognomonic for MM and may also be seen in other diseases that affect the marrow. In general, however, MM is suspected whenever MR images depict an expansile focal mass; multiple focal masses in the axial skeleton; diffuse marrow involvement, particularly at known sites of normal hematopoiesis; or multiple compression fractures in a patient with no known primary malignancy.

In patients with newly diagnosed MM, several MR patterns have been described that define tumor burden (25,28,30, 71,72) (Fig 6). Low tumor burden is normally associated with a normal MR pattern. On the other hand, high tumor burden is suspected when marrow is diffusely hypointense on T1-weighted im-

Figure 6 (continued). MR imaging patterns in MM. (d, e) Left: T1-weighted spin-echo images (400/15). Middle: STIR images (2,000/150/20). Right: Gadolinium-enhanced fat-suppressed T1-weighted spin-echo images (500/15). (d) Diffuse speckled marrow involvement in thoracic spine. Note nodular abnormalities in entire spine are better seen on STIR and gadolinium-enhanced images. Speckled, or salt-and-pepper, appearance is better appreciated on STIR and gadolinium-enhanced images, again with posterior-element lesions better seen on these images. (e) Focal disease in thoracic spine. Note several focal lesions at T3 and T4 spinous processes and T12 vertebral body. The smaller spinous process lesions at T4 (arrows) can be seen only on STIR and gadolinium-enhanced images.
FRACTURE IN MM

Spinal compression fractures occur in 55%–70% of patients with MM (82) (Figs 2, 9). These fractures may be due to bone destruction by a focal mass or to increased osteolysis. MR imaging provides an opportunity to detect the offending cause (83,84). Lecouvet et al (82) classified spinal fractures into benign or malignant, primarily on the basis of the presence of an associated focal mass. Sixty-seven percent of 224 total fractures in 37 patients were identified as benign. In our review of MR imaging surveys of the entire spine in 264 patients with newly diagnosed MM (84), fractures were present in 117 (44.3%). A single fracture was seen in 50 (42%) of 117 patients, and a focal lesion causing the fracture was seen in 40 (80%) of those 50 patients. In patients with multiple fractures, 273 sites of fracture were seen in 67 (58%) patients; of the 273 fractures, 126 (46%) had an associated mass. These results indicate that spinal fractures in MM do not require the presence of a focal mass and can occur in a setting of marrow that appears benign on MR images (82–84). Tricot (21) proved this point in laboratory studies that showed that the presence of my...
eloma cells in bone marrow stroma increases the formation of osteoclast-activating factors, leading to increased bone resorption and subsequent fractures.

Spinal fractures also occur following treatment. Moulopoulos et al (79) reported 35 new sites of fracture in 29 successfully treated MM patients. In patients with relapse, fractures were also noted. In another study, Lecouvet et al (85) showed 131 new fractures in 37 patients undergoing therapy. They found that the group of patients with an initial MR study showing diffuse disease or more than 10 focal lesions had a shorter fracture-free interval than did the patients who did not have diffuse disease shown on MR images. They suggested that the initial MR study may help identify patients at increased risk for subsequent fracture of the spine. Currently, bisphosphonates are standard drugs administered to MM patients undergoing therapy, because these drugs are known to decrease the incidence of compression fractures. Bisphosphonates disrupt the vicious cycle of increased osteolysis and myeloma cell production.

New treatment methods for spinal fractures related to MM include percutaneous vertebroplasty and kyphoplasty. Percutaneous vertebroplasty is now accepted as a method of alleviating the bone pain associated with a spinal fracture (86). The procedure also has the secondary aim of preservation of the remaining height of the vertebral body. Kyphoplasty, on the other hand, aims at restoration of the original vertebral height and elimination of spinal deformity (87). MR findings of abnormal signal intensity in spinal fractures aid the interventionalist in determining the treatment level in cases of multiple spinal fractures. Parallel zones of hypointensity on T1-weighted images and hyperintensity on STIR or T2-weighted images in the fractured vertebra correlated with localized pain during percussion at the site of fracture.

**COMPLICATIONS AND PROGRESSION OF DISEASE**

The multiple drug therapies currently utilized in the treatment of MM result in complications that are identifiable on MR images. High doses of corticosteroids, a frontline drug in treatment of MM, may cause spinal fracture and avascular necrosis of the femoral heads. Immunosuppression caused by cytotoxic drugs results in a higher incidence of infections in the spine (eg, discitis) and the brain (eg, cerebritis, cerebral abscess). Cyclosporine used in marrow transplantation regimens may result in neurologic changes of posterior reversible cerebral encephalopathy.

A rare progression in MM is leptomeningeal spread within the central nervous system. In a recent review of 1,856 treated patients at our institution, Fassas et al (88) showed this complication in 18 patients. MR findings of leptomeningeal enhancement in the brain or spine were seen and helped establish the diagnosis (Fig 10). The definitive diagnosis was made with results from cytologic analysis of cerebrospinal fluid. This complication was associated with unfavorable cytogenetic results such as chromosome 13 deletion, histologic findings of plasmablastic cells, other extramedullary sites of disease, and plasma cell leukemia. Myelofibrosis and amyloidosis can develop as a consequence of treatment in patients with MM. Myelofibrosis can be suggested on MR studies as a conversion of the entire bone marrow to diffuse hypointensity on both T1-weighted and STIR images. Amyloidosis can be seen as focal areas of hypointensity on both T1-weighted and STIR images.

Relapse and poor response to treatment are well evaluated with MR imaging. In patients with clinical relapse, new focal lesions or an increase in the size of previously identified focal lesions in
medullary or extramedullary sites are seen (Fig 11). In severe relapse, conversion of a normal pattern to one of diffuse involvement may also be seen. Poor response to treatment protocols also can be demonstrated on follow-up MR studies, where they appear as no change or deterioration in the previously identified areas of involvement.

MGUS AND SOLITARY BONE PLASMACYTOMA

Monoclonal gammopathy of uncertain significance (MGUS) is the most common cause of laboratory-discovered monoclonal gammopathy. MGUS is usually an incidental finding, and its incidence in patients over the age of 70 years is 3% (89). The serum M protein component is typically low, Bence-Jones proteinuria is rare, and there is less than 10% plasmacytosis in the marrow. M protein levels remain relatively stable over time. Although most patients die of comorbid conditions, MGUS can “evolve” to MM, Waldenström macroglobulinemia, chronic lymphocytic leukemia, plasmacytoma, amyloidosis, or lymphoma. The longer the follow-up, the higher the percentage of patients whose condition eventually progresses to malignant disease. In a recent study of almost 1,400 patients with MGUS and with 11,000 person-years of follow-up, the cumulative probability of progression was 12% at 10 years, 25% at 20 years, and 30% at 25 years (90). Initial monoclonal protein (M protein) concentration was a significant predictor of progression at 20 years. Vande Berg et al (91) performed MR imaging in 35 patients with MGUS and found MR abnormalities in seven. Of the patients with no MR abnormalities, none required treatment after a follow-up of 30 months. On the other hand, four of seven patients with abnormal MR findings required treatment within 5 years of diagnosis. MR imaging provides important information concerning prognosis in patients with MGUS, and an abnormal MR study warrants closer follow-up for signs of progressive disease.

Solitary bone plasmacytoma is uncommon (representing 2%–3% of plasma cell dyscrasias) and usually manifests with bone pain. The diagnosis is based on histologic evidence of tumor consisting of monoclonal plasma cells. Associated laboratory findings include normal blood levels of hemoglobin, creatinine, and calcium, with negative bone marrow biopsy results and skeletal radiographic survey findings.

A small, if any, M protein component should decrease with treatment (definitive local radiation therapy) (92). The rate of reduction of M protein level may be slow (93), and in many patients the M protein persists for years despite adequate radiation therapy, implying the presence of tumor cells beyond the radiation field. The median overall survival after radiation therapy in patients with solitary bone plasmacytoma is 10 years. The median time to progression to MM is 2–3 years. In some studies, the size of the lesion, osteopenia, and low levels of uninvolved immunoglobulins were predictive of progression to overt MM (94). Results of several studies indicated that screening of patients with solitary bone plasmacytoma by using MR imaging or in combination with a skeletal radiographic survey revealed a high prevalence of other plasmacytomas. This group of patients also showed a shorter latency of progression to MM (95–97).

Figure 10. Leptomeningeal spread in MM. Contrast-enhanced sagittal (left) and transverse (right) T1-weighted spin-echo (450/15) MR images of lumbar spine show abnormal enhancement of nerve roots (arrowhead) and surface of conus medullaris (arrow). Transverse image shows distinct nodular enhancement of the cauda equina, indicative of leptomeningeal spread of tumor.

Figure 11. Extramedullary spread in MM. Left: Transverse T2-weighted spin-echo MR image (2,000/80) in a patient with clinical findings of relapse show a mass (curved arrow) in the left pararenal space. A separate mass (straight arrow) is in the right pararenal space. Right: On transverse T2-weighted (2,000/80) section obtained at a lower level, right pararenal mass is shown extending into adjacent right neural foramen and epidural space (arrowhead). Associated dural sac compression is noted. Biopsy of both masses revealed malignant plasma cells.
MR-DIRECTED CT-ASSISTED SKELETAL BIOPSY

Cytogenetic abnormalities (in particular, chromosome 13 deletion) in the plasma cells in patients with MM is an important negative predictor of durable clinical response and overall survival (17). Obtaining proper biopsy specimens of the tumor that can lead to this discovery has become a necessary clinical tool. MR survey studies that depict unsuspected sites of focal lesions help direct this process of specimen collection (Fig 12). Bone biopsies with large-bore needles (generally 12–14-gauge bone biopsy needles) are difficult to perform in the MR setting. CT guidance of these MR-depicted focal lesions has aided the safe performance of these procedures, especially in spinal bone biopsies. Our experience with biopsies of the spine and pelvis of MR-depicted focal lesions has led to a 20% increase in the yield of positive cytologic and cytogenetic information from biopsies at these sites, compared with results in samples obtained from random iliac crest biopsies (37). This had led to a more aggressive clinical approach once cytogenetic abnormalities are detected.

REFERENCES


CONCLUSION

In the past decade, important advances in the understanding of MM and the therapeutic options available to patients with the disease have resulted in improved patient survival. This has gone hand in hand with the advanced capabilities of modern imaging methods, particularly MR. MR imaging bone marrow surveys in patients with MM demonstrate the broad spectrum of involvement, the results of treatment, the areas of potential complications, and the sites of focal disease for safe bone biopsies. 

Figure 12. MR-directed CT-assisted biopsy. Left: Sagittal contrast-enhanced fat-suppressed T1-weighted spin-echo (600/15) MR image shows two enhancing lesions at T3 (arrow) and T9 (arrowhead). Right: Transverse CT image obtained with patient in prone position during CT-assisted biopsy of the T9 lesion shows biopsy needle (arrow) entering the lytic lesion of T9 vertebral body by using a transpedicular approach.


