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Multiple Myeloma: Primary Bone Tumor with Systemic Manifestations

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Multiple myeloma is a multifocal plasma cell neoplasm that commonly involves the spine. It is the most common plasma cell neoplasm and represents 10% of all hematologic malignancies diagnosed in the United States, with an annual incidence of 16,000 new cases [1]. Most patients are older than 60 years of age. Systemic complications include skeletal, hypercalcemia, anemia, infections, renal failure, and neurologic manifestations.

Presentation

Skeletal complications of multiple myeloma are common, with greater than 70% of patients presenting with bone pain at diagnosis. Review of plain radiographs shows that approximately 80% of patients who have multiple myeloma have lytic lesions, osteoporosis, or fractures. More than 50% of patients who have multiple myeloma present with spinal compression fractures resulting from tumor infiltration or osteoporosis [2]. Other spinal sequelae are neurologic deficits, including myelopathy or radiculopathy, which may result from vertebral body fractures or epidural soft tissue tumor growth into the spinal canal. Additionally, patients may develop neuropathy as a direct result of the disease or complications from treatment.

The median survival in patients presenting with multiple myeloma is 4 years, but advanced treatments have had a major impact on reducing the morbidity and mortality related to the systemic and spine complications from this disease. Newer chemotherapeutic agents, such as bortezomib (Velcade), thalidomide (Thalomid), and lenalidomide (Revlimid), have led to improved survival [3]. The combinations of high-dose chemotherapy and autologous or allogeneic transplantation have also improved survival [4–6].

Medical advances in treating skeletal complications, such as bisphosphonate therapy, have been shown to decrease skeletal-related events (SREs) resulting from multiple myeloma [7]. Additionally, percutaneous injections of polymethylmethacrylate (PMMA) by means of vertebroplasty or kyphoplasty into vertebral body pathologic or osteoporotic fractures have improved the quality of life in patients who have multiple myeloma. Open surgery remains difficult because of the presence of diffusely osteoporotic bone, which is a hallmark of this disease; however, bone cement augmentation of the instrumented spine may improve outcomes in these patients.

Pathophysiology

In multiple myeloma, malignant transformation of a plasma cell results in the secretion of monoclonal immunoglobulins. Plasma cells are derivatives of B cells found in the bone marrow and secrete immunoglobulins used for humoral immunity. The pathophysiology of the malignant transformation of plasma cells resulting in

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a monoclonal gammopathy is unclear but may result from chronic antigenic stimulation. Ultimately, the plasmacytosis replaces normal bone marrow elements and undergoes hematogenous metastases. The replacement of normal marrow elements results in anemia and, less commonly, thrombocytopenia. The increased infection risk in a patient who has multiple myeloma results from a decreased number of normal plasma cells.

Osteolysis and osteoporosis are major sources of skeletal morbidity in patients who have multiple myeloma. Osteolysis results from dissociation between bone resorption and deposition. In multiple myeloma, osteoclasts are preferentially activated, causing bone destruction, whereas osteoblasts are inhibited. Osteoclast activation involves the nuclear receptor factor-κB (RANK), which is the ligand for RANK (RANKL) and osteoprotegerin. RANK is expressed on the surface of osteoclast lineage cells and is upregulated by binding RANKL secreted from bone marrow stromal cells and osteoblasts [7–14]. Multiple myeloma cells induce stromal cells to secrete cytokines, such as interleukin (IL)-6, tumor necrosis factor (TNF)-β, and insulin-like growth factor. These cytokines upregulate RANKL expression, inducing osteoclastogenesis and bone destruction. This osteolysis increases cytokine expression, thus perpetuating the cycle. Osteoprotegerin normally inhibits RANK-RANKL signaling, but the level of osteoprotegerin is markedly decreased in patients who have multiple myeloma. This process also leads to increased osteoclast activation and subsequent osteoporosis.

In addition to osteoclast activation, multiple myeloma results in osteoblast inhibition. This inhibition prevents osteogenesis, adding significantly to the resultant lytic destruction of bone. Recent evidence suggests that gene expression of dickkopf 1 (DKK1) inhibits the Wnt signaling pathway that is essential for the growth and differentiation of osteoblasts [15–17]. Increased expression of DKK1 has been associated with lytic bone destruction in patients who have multiple myeloma [18].

Laboratory evaluation

For patients suspected of harboring multiple myeloma, serum and urine electrophoresis is assessed for a monoclonal hypergammaglobulinemia or Bence-Jones protein, respectively. The most common protein spike detected on serum examination is IgG, followed by IgA. In 80% of patients, a localized protein spike is detected, whereas 20% have a hypogammaglobulinemia or no apparent spike. Other laboratory abnormalities may include hypercalcemia, hyperuricemia, an elevated erythrocyte sedimentation rate, and elevated alkaline phosphatase. Fragmentation of immunoglobulins may result in the presence of Bence-Jones protein detectable in the urine.

Biopsy or bone marrow aspirate

Biopsy of discrete bone lesions can establish the diagnosis of a plasmacytoma or collection of monoclonal plasma cells. To establish the diagnosis of multiple myeloma, multiple sites of abnormal plasma cells must be present. This is in counterdistinction to plasmacytoma, in which the plasma cell dyscrasia occurs at a single site. A bone marrow aspirate, such as from the iliac crest, is important for establishing the diagnosis of multiple myeloma and differentiating it from other cytopenias or blood cell dyscrasias. A diagnostic bone marrow aspirate is present with greater than 15% plasma cells present in the aspirate.

Imaging

Having established the diagnosis of a monoclonal gammopathy, a complete bone survey is ordered to assess for additional skeletal lesions suggestive of multiple myeloma. Multiple myeloma often presents with ''punched-out'' lesions in the bone. A bone survey consists of plain radiographs of the complete spine, skull, ribs, pelvis, and long bones of the upper and lower extremities. Approximately 80% of patients have additional lytic lesions, 10% have generalized bone demineralization, and 10% have normal findings. In patients who have multiple myeloma, the most common fracture sites are at the thoracolumbar junction. Although a bone scan is frequently used to assess for metastatic bone involvement, it is not useful in the assessment of patients who have multiple myeloma. Bone scans detect osteoblastic activity in response to a stimulus, such as a tumor. As noted, multiple myeloma manifests a limited osteoblastic reaction, and thus is subject to a high false-negative rate.

Although skeletal surveys have historically been used to screen for multiple myeloma, MRI

has become the diagnostic test of choice in assessing the spine [19]. Sensitive imaging sequences for detecting tumor are T1-weighted and T2 short tau inversion recovery (STIR) images. On T1-weighted images, tumor is hypointense to normal marrow signal, and on T2 STIR images, tumor is hyperintense. T2-weighted images show variable signal intensity, but axial images are routinely used to assess the degree of epidural spinal cord compression. Recently, whole-body MRI scans have been introduced to assess for marrow involvement of several cancers, which may ultimately improve the ability to screen for myeloma [20,21].

CT scans are often used to delineate the degree of bone destruction in patients with lytic destruction detected on plain radiographs. Whole-body helical multidetector CT (MDCT) scans may be the most sensitive test for identifying small osteolytic lesions. Additionally, MDCT scans provide an excellent assessment of cortical and cancellous bone involvement and fracture risk [22].

18F-fluorodeoxyglucose (FDG) positron emission tomography (PET) is not wholly reliable in identifying myelomatous lesions but may add information about additional sites of bone disease [23]. Recently, 11C-choline PET was compared with 18-FDG PET for screening patients who have multiple myeloma. 11C-choline PET may ultimately prove to be more sensitive for identifying marrow tumor involvement [24,25].

Medical treatment: reduction of skeletal-related events

Medical therapy using bisphosphonates decreases SREs in patients who have multiple myeloma. Bisphosphonates are synthetic derivatives of pyrophosphates that reduce bone complications. These agents inhibit osteoclast activity, and thus reduce or inhibit further bone resorption; however, bisphosphonates do not promote the deposition of new bone. As noted, multiple myeloma inhibits osteoblast differentiation; thus, the net effect of bisphosphonates may be solely to prevent further bone destruction. Additionally, they result in apoptosis of myeloma cells [26].

Oral bisphosphonates are not generally effective. The intravenous preparations used to treat multiple myeloma include zoledronic acid (4 mg) and pamidronate (90 mg) administered every 3 to 4 weeks. Although zoledronic acid is more expensive, the injection can be given in 15 minutes compared with 2 hours for pamidronate. Clodronate and ibandronate are two additional bisphosphonates that have been explored in European studies for patients who have multiple myeloma.

Several randomized trials have proved the efficacy of bisphosphonates in preventing SREs, such as spine fractures. Berenson and colleagues [27] reported the results of the Myeloma Aredia Study Group, in which 392 patients were randomized to receive placebo or pamidronate every 4 weeks for 21 cycles. SREs were defined as pathologic fractures, the need for radiation therapy (RT) or surgery, or progression to spinal cord compression. At 21 months of follow-up, the mean number of annual SREs was 2.1 in the placebo group compared with 1.1 in the pamidronate group ($P = .008$). The median time to the first SRE was 10 months in the placebo group and 21 months in the pamidronate group ($P < .001$).

Rosen and colleagues [28] reported a randomized controlled trial of 1648 patients, of whom 513 had multiple myeloma, comparing zoledronic acid with pamidronate. The median time to the first SRE was not statistically different between the two groups, demonstrating the noninferiority of zoledronic acid.

McCloskey and colleagues [29,30] reported the result of clodronate in a prospective randomized trial comparing clodronate with placebo in 536 patients. The rate of vertebral body fractures was significantly lower in the clodronate cohort compared with placebo, (38% versus 55% [$P < .01$], respectively). Conversely, a prospective randomized trial showed no difference between ibandronate and placebo at 24 months.

The American Society of Clinical Oncology has published practice guidelines for the administration of bisphosphonates in patients who have multiple myeloma [31]. Zoledronic acid or pamidronate is recommended for patients with lytic bone destruction or compression fracture from osteopenia. Additionally, patients who have diffuse osteopenia based on plain radiographs or a bone mineral density test in the absence of lytic disease or compression fractures are recommended to start therapy. Patients who have solitary plasmacytoma or monoclonal gammopathy do not require treatment. Biochemical markers of bone metabolism, such N-telopeptide and alkaline phosphatase, are not routinely used to monitor therapy.

Patients on bisphosphonates are monitored for renal failure with monthly serum creatinine concentrations before administration of therapy.

Patients are also monitored every 3 to 6 months for proteinuria. Other routine blood tests include calcium, magnesium, and hemoglobin. Adverse side effects from bisphosphonates include transient myalgias, arthralgias, and flu-like symptoms.

Recently, osteonecrosis of the jaw (ONJ) has been described in conjunction with bisphosphonates. Zervas and colleagues [32] reported a 9.5-fold increase in this complication using zoledronic acid compared with pamidronate. To date, the role of bisphosphonates remains unclear in the genesis of ONJ, because most patients are additionally receiving chemotherapy, radiation, and steroids. Some patients who have ONJ have poor dentition or recent dental work. Patients may benefit from pretreatment comprehensive dental care.

Surgical and radiation treatment: spine decision making in multiple myeloma

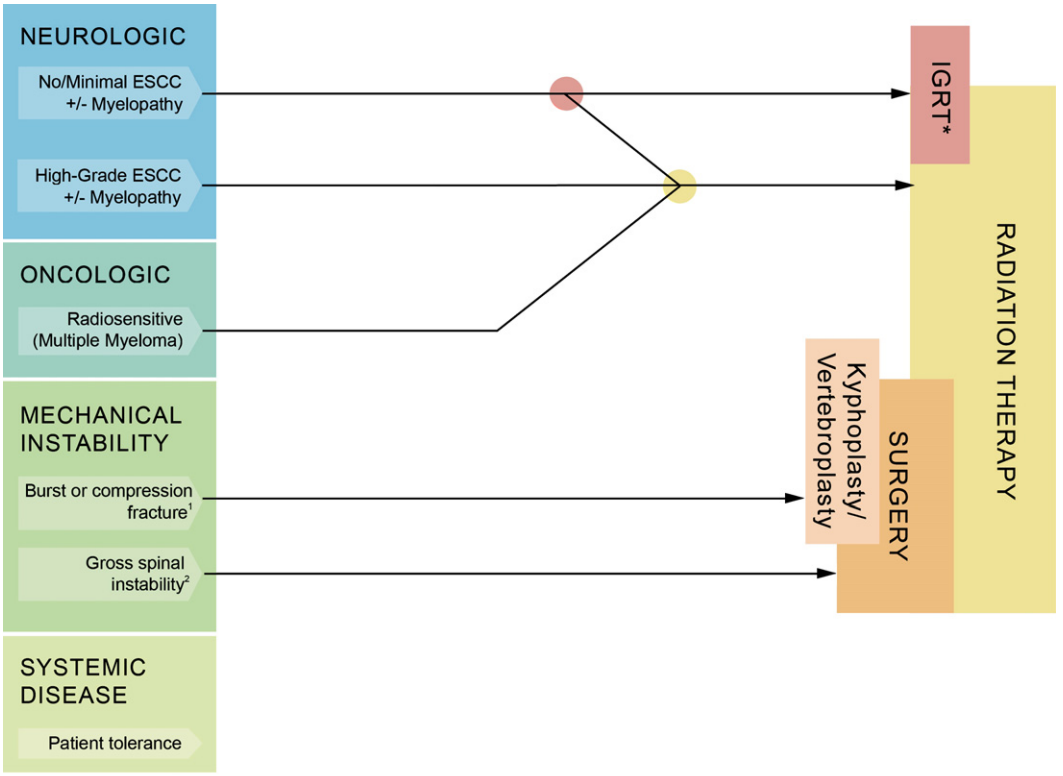
Decision making in the treatment of multiple myeloma reflects four fundamental assessments: neurologic, oncologic, mechanical instability, and systemic disease. This framework, referred to as "NOMS," helps to delineate among three fundamental treatment considerations: chemotherapy, RT, and surgery [33]. The neurologic assessment (N) includes the presence of myelopathy, radiculopathy, and the severity of epidural spinal cord compression. The oncologic assessment (O) reflects the radio- and chemosensitivity of the tumor. Mechanical instability (MS) assesses the ability of the spine to resist physiologic loads, the degree of movement-related pain in combination with radiographic criteria. Systemic disease (S) reflects the extent of disease and medical comorbidities (Fig. 1).

The neurologic and oncologic assessments are made in combination. Patients who have multiple myeloma rarely present with significant epidural disease or myelopathy (N) [34]. This observation may reflect that patients often present for medical care because of severe bone pain, biologic or instability, before the development of epidural extension [34]. High-grade epidural spinal cord compression is often an indication for surgery in patients who have radioresistant solid tumors, such as colon or lung carcinoma. This fact was recently borne out in a prospective randomized trial comparing surgery and radiation with radiation alone, in which surgery and radiation were found to be superior in terms of rates of maintenance and recovery of ambulation and survival [35]. The blood dyscrasias (ie, multiple myeloma, lymphoma), were excluded from this study because of their extreme radiosensitivity. Radiation causes apoptosis of multiple myeloma cells, resulting in immediate resolution of the tumor and consequent spinal cord compression. Thus, in patients who have multiple myeloma with vertebral body disease, even in the presence of high-grade epidural spinal cord compression, the initial treatment is RT. Low-dose radiation (eg, 20 Gy in 10 fractions) is often sufficient to resolve biologic pain and spinal cord compression. In the absence of high-grade spinal cord compression, consideration can be given to treatment with single-fraction stereotactic radiosurgery (SRS) delivered by means of image-guided intensity-modulated RT or a Cyberknife. In candidate patients, SRS allows patients to start systemic therapy sooner. Patients with high-grade spinal cord compression are excluded from consideration of SRS because of the risk for spinal cord injury. In addition to radiation, patients are routinely considered for chemotherapy as an initial treatment. In these cases, radiation may be delayed until patients show symptomatic bone progression.

Because of the radio- and chemosensitivity of multiple myeloma, most decisions regarding the need for surgical intervention are based on assessments of mechanical instability rather than on neurologic and oncologic issues. Mechanical instability reflects significant osteolytic bone destruction reflective of the tumor destruction and diffuse osteoporosis seen in many patients. Osteolysis may result in burst or compression fractures that can cause severe axial load pain and progressive spinal deformity. Conversely, pain from many myelomatous or osteoporotic fractures resolves within a week, requiring no intervention.

Vertebroplasty/kyphoplasty

For patients with ongoing pain from fractures, decisions regarding percutaneous vertebral augmentation, such as vertebroplasty or kyphoplasty, versus open surgical decompression and instrumentation are required. Patients who have multiple myeloma with a burst or compression fracture of the middle to lower thoracic or lumbar spine and ongoing axial load pain are considered for percutaneous vertebral body augmentation. Relative contraindications to these procedures include a breach of the posterior vertebral body



[1] Axial load pain in the absence of gross instability

[2] (a) Atlanto - axial: >3.5mm subluxation >11° angulation or >5mm subluxation
(b) Subaxial cervical: burst or compression with extension into unilateral joint
(c) Thoracic: burst or compression with extension into unilateral joint
(d) Lumbar: mechanical radiculopathy

* Image-Guided Radiation Therapy

Fig. 1. Neurologic, oncologic, mechanical instability, and systemic disease (NOMS) decision framework as applied to multiple myeloma. ESCC, epidural spinal cord compression.

cortex and significant epidural disease (Fig. 2). Additionally, these procedures are difficult to perform in the cervical and upper thoracic levels because of anatomic constraints and difficulty with imaging. Cases of transoral cement augmentation of the C2 vertebral body have been reported [36].

Significant pain improvement has been reported using vertebroplasty or kyphoplasty in treating pathologic fractures from multiple myeloma. Dudeney and colleagues [37] reported the results of 55 kyphoplasty procedures used to treat osteolytic compression fractures in 18 patients who had multiple myeloma. At a median follow-up of 7.4 months, there was significant improvement in the Short Form 36 (SF36) scores for bodily pain (23.2–55.4; $P = .0008$), physical function (21.3–50.6; $P = .0010$), vitality (31.3–47.5; $P = .010$), and social functioning (40.6–64.8; $P = .014$). A median of 34% of vertebral body height restoration was achieved. Complications were minimal, including two cases of asymptomatic cement leakage.

Cotten and colleagues [38] reported 40 percutaneous vertebroplasty procedures in 37 patients for pathologic fractures, 10 of which were multiple myeloma. Partial or complete pain relief was achieved in 36 of 37 patients. In this study, there was no correlation between the amount of vertebral body filling and pain relief. This suggests that the pain relief does not result solely from stabilization of microfractures and reduction of mechanical forces. Destruction of pain

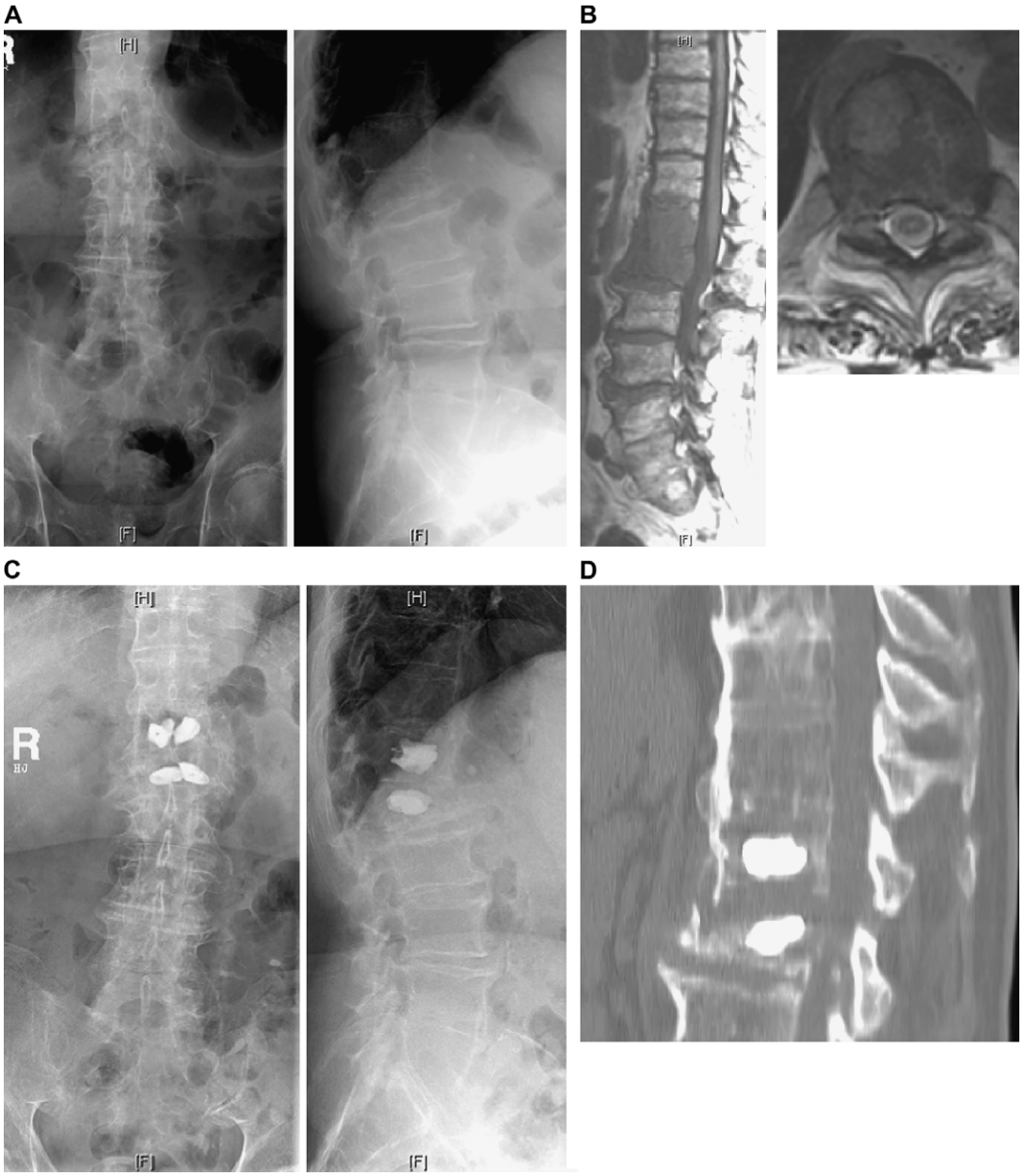


Fig. 2. An 86-year-old man presented with acute onset of pain and was unable to sit or ambulate. (*A*) L1 burst fracture. (*B*) MRI showed T12-to-L1 infiltrated marrow disease with no significant epidural compression. The patient underwent a needle biopsy, confirming plasma cell neoplasm. Serum protein electrophoresis confirmed an IgG spike, and an iliac crest biopsy showed greater than 15% plasma cells. Given the patient's advanced stage and comorbidities and the difficulty in holding spinal fixation in patients who have multiple myeloma, he was dispositioned to undergo kyphoplasty for pain control. (*C*) Anteroposterior and lateral views show the kyphoplasty placement of PMMA. (*D*) CT reconstruction shows the kyphoplasty placement of PMMA. The patient had significant pain resolution from severe to mild, and he was able to ambulate assisted. He underwent 20 Gy in 10 fractions, followed by thalidomide chemotherapy.

fibers from mechanical, thermal, and chemical forces from the methylmethacrylate injection may play a role. In this series, all patients underwent postprocedure CT scans. Leaks were identified in the spinal canal (15 leaks), neural foramina (8 leaks), intradiscal (8 leaks), paravertebral tissues (21 leaks), and lumbar venous plexus (2 leaks). Two patients required open surgery for radiculopathy resulting from neural foraminal extravasation. Of the 15 procedures resulting in epidural extension of PMMA, 13 had a breach of the posterior cortex and 10 had epidural disease.

Hentschel and colleagues [39] reported a large series from M.D. Anderson Cancer Center of 132 treatment levels in 66 patients, of whom 35 (53%) were treated for pathologic fractures related to multiple myeloma. Pain scores as assessed by the visual analog scores were significantly improved from 8 (severe pain) to 2 (mild pain). Eighteen levels treated in 17 patients had relative contraindications to kyphoplasty or vertebroplasty. There were complications in 7 (39%) of 18 levels in this group compared with 12 (11%) of 114 levels in the group with no contraindications. The major complication was extravasation of cement anterior to the vertebral body, and no patient required an open operation.

With the encouraging result using percutaneous vertebral body augmentation, few patients require open surgical procedures for destructive lesions causing gross instability. Of the 1020 patients operated on for metastatic tumors at Memorial Sloan-Kettering Cancer Center over the past 12 years, only eight operations have been for multiple myeloma, reflecting the rare indication for open surgery in this patient population. In the authors' practice, instability requiring an open operation is severe movement-related pain in conjunction with radiographic criteria. Radiographic determinants of instability are level dependent. In the atlantoaxial spine, patients present with flexion, extension, and rotational pain in combination with fracture subluxation greater than 5 mm or greater than 3.5 mm of subluxation and 11° of angulation (Fig. 3). These patients often require an occipital cervical fixation procedure to provide stability before radiation or chemotherapy. Instability requiring open surgery of the cervical and thoracic spine typically presents with a burst or compression fracture with extension into a unilateral joint. Lumbar spine fractures rarely require an open operation, with the exception being patients who present with mechanical radiculopathy (ie, radicular pain on axial load).

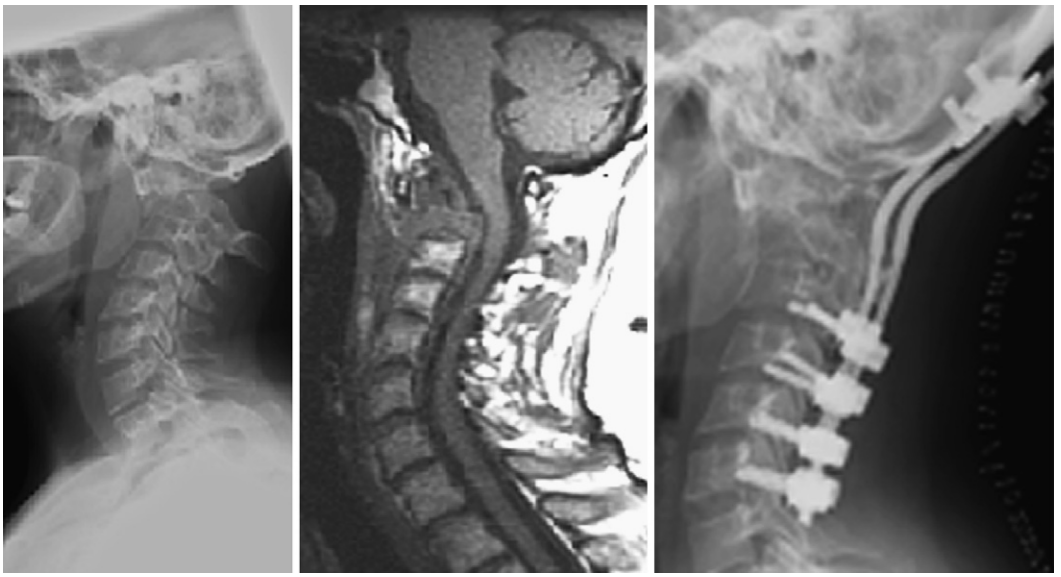


Fig. 3. A 64-year-old man with a known history of multiple myeloma. He presented with acute onset of rotational and flexion extension pain. Plain radiographs show erosion of C2 and C3 vertebral bodies with a C1-to-C2 6-mm fracture subluxation and 20° of angulation. MRI showed no evidence of epidural disease. Based on radiographic criteria, the patient was grossly unstable. He underwent an occipital C6 fusion with complete resolution of neck pain.

The presence of diffuse osteoporosis or osteopenia in addition to osteolytic bone marrow in patients who have multiple myeloma makes instrumentation more difficult in this patient population compared with other tumors. Rao and colleagues [34] reviewed a series of 35 patients treated for cervical spine disease. In this series, 19 of 20 patients had pain resolution with radiation alone at a median dose of 25 Gy in 10 fractions. An additional 6 patients were irradiated but did not have long-term follow-up. Patients with minimal deformity were irradiated in an external orthosis. Of note, some patients showed radiographic healing of the osteolytic fractures. Eight patients underwent surgery: 6 underwent surgery and radiation, and 2 underwent surgery alone. Of these 8 patients, 2 (25%) experienced construct failure, which was attributed to progression of disease at adjacent segments or to the poor quality of myelomatous bone.

Because of the uniquely poor quality of bone in patients who have myeloma, instrumentation strategies may need to be altered. Multiple myeloma predominantly affects the bone marrow and vertebral bodies. Additionally, treatment with steroids and radiation puts the patient at increased risk for osteoporosis at spinal fixation points. For this reason, stand-alone anterior constructs may have a higher failure rate than circumferential fixation. Additionally, pedicle screw augmentation with PMMA may improve posterior fixation. Chakrabarti and colleagues [40] recently reported a salvage technique using transpedicle vertebroplasty in two patients who had posterior instrumentation for the treatment of compression fractures at the thoracolumbar junction. Both patients had complete pain resolution after percutaneous reconstitution of the anterior column.

Summary

Multiple myeloma is a systemic plasma cell dyscrasia that frequently affects the spine. Patients often manifest a protein spike on serum protein electrophoresis and Bence-Jones proteins in the urine. Radiographic workup includes a skeletal survey, but a bone scan frequently produces false-negative results because of the inhibition of osteoblasts. MRI is the most sensitive imaging modality for marrow involvement of the spine, whereas high-resolution CT scans can detect marrow involvement and predict fracture risk. 18-FDG PET may pick up additional spinal lesions. 11C-choline PET is now being explored for early detection.

For symptomatic lesions involving the spine, the treatment is often a combination of low-dose radiation and chemotherapy. Intravenous bisphosphonates have been shown to decrease SREs in patients who have osteolytic lesions or diffuse osteoporosis. Percutaneous vertebral augmentation, such as vertebroplasty or kyphoplasty, improves symptoms in patients who have symptomatic compression fractures. Open decompression and fixation are rarely indicated in this population because of the high chemo- and radiosensitivity of these lesions. The osteoporosis and osteolysis present in the vertebral bodies of patients who have myeloma makes fixation more tenuous than in patients who have other tumors.

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