Multiple Myeloma Invasion of the Central Nervous System

Keith O. Schluterman, MD; Athanasios B.-T. Fassas, MD; Rudy L. Van Hemert, MD; Sami I. Harik, MD

Background: Although neurologic manifestations often complicate the course of patients with multiple myeloma (MM), direct central nervous system invasion is rare.

Objective: To describe the neurologic symptoms and signs, imaging, cerebrospinal fluid findings, and the clinical course of patients with central nervous system myeloma invasion, all of whom had leptomeningeal myelomatosis.

Design and Participants: Review of 23 patients with MM and leptomeningeal myelomatosis proven by malignant plasma cells in their cerebrospinal fluid.

Setting: Tertiary-care university medical center.

Results: Twenty-one patients had advanced-stage MM. Leptomeningeal myelomatosis was diagnosed up to 29 months (median, 13 months) after diagnosis of MM. Symptoms precipitating neurologic evaluation included manifestations of diffuse cerebral dysfunction, cranial nerve palsies, and spinal radiculopathies. Cerebrospinal fluid was abnormal in all patients, usually exhibiting pleocytosis and elevated protein content, plus positive cytologic findings. Specific magnetic resonance imaging findings suggestive of central nervous system invasion were found in 70% of the patients. These included leptomeningeal contrast enhancement and evidence of meningeal-based lesions sometimes masquerading as intraparenchymal lesions. Despite aggressive systemic and local treatment, the outcome was poor, reflecting the aggressiveness of the underlying MM.

Conclusion: Leptomeningeal myelomatosis, although rare, should be considered in patients with MM and symptoms suggestive of widespread nervous system involvement.

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Patients with multiple myeloma (MM) often have neurologic complications. These include peripheral neuropathies, spinal radiculopathies, cranial nerve palsies, spinal cord compression, and a host of metabolic encephalopathies. The causes include vertebral compression fractures, base of skull and other bony involvement, metabolic derangements (eg, hypercalcemia and uremia), hyperviscosity syndrome, and amyloidosis, in addition to the toxicity and complications of treatment. While infiltration of the leptomeninges by various malignancies is well known, invasion of the central nervous system (CNS) in MM is rare, either as presumed intracerebral metastases or as leptomeningeal myelomatosis (LMM), with approximately 70 cases reported in the English-language literature in the past century, mostly case reports.

Our institution has emerged as a leading center for the intensive treatment of MM with high-dose chemotherapy followed by autologous or allogeneic peripheral blood stem cell or bone marrow transplants. We identified 23 patients with CNS invasion by MM for whom proof of invasion was ascertained by positive cerebrospinal fluid (CSF) cytologic findings. We now describe the spectrum of the clinical neurologic, CSF, and neuroimaging findings in these patients and the autopsy findings in 2. A prior publication from our institution on 18 of the 23 patients and an invited review primarily focused on the association of LMM with the hematologic characteristics of the disease, but did not address in detail the neurologic aspects.

METHODS

Approximately 2000 patients with MM were treated at the University of Arkansas Medical Center between August 1990 and April 2003.
Most of them received high-dose chemotherapy and later peripheral blood stem cell or bone marrow transplants. Retrospective review of records identified 23 patients with positive CSF cytologic findings for malignant plasma cells (Figure 1). Cerebrospinal fluid examination was performed because of clinical features suggestive of CNS involvement.

Initial neurologic symptoms were defined as the symptom(s), suspicious for CNS involvement, that prompted neurologic evaluation and CSF examination. Neurologic findings were the pertinent findings on neurologic examination, usually performed by a staff neurologist, at the time of diagnosis of LMM. Sites of neurologic dysfunction were categorized into 3 axes: cerebral, cranial nerve, and spinal nerve root, based on initial and subsequent neurologic symptoms and signs. All pertinent neuroimages were reviewed. Many patients had multiple CSF examinations, but we report the results obtained from the first examination that provided the diagnosis of LMM.

### RESULTS

#### PATIENT DEMOGRAPHICS AND DISEASE CHARACTERISTICS

There were 13 men and 10 women with LMM. Their median age at diagnosis of MM was 54 years. Eleven patients had IgG, 7 had IgA, 3 had light chain, 1 had non-secretory, and 1 had biclonal (IgG and IgA) MM. None had IgM MM. Twenty-one patients had Salmon-Durie stage III disease at diagnosis and only 2 had stage II disease. The median interval between diagnosis of MM and diagnosis of LMM was 13 months; the longest interval was 29 months. Only 1 patient was diagnosed with LMM as the initial manifestation of MM. At the time of diagnosis of LMM, 3 patients had complete remission, 5 had near-complete remission, 6 had partial response, and 9 had progressive disease despite treatment as defined previously.15

#### CLINICAL NEUROLOGIC FEATURES

At the time of diagnosis of LMM, there was a diffuse array of neurologic symptoms and signs (Table). Fifteen patients (65%) had cerebral symptoms, including headache, mental status changes, and seizures. Twelve patients (52%) had neurologic findings referable to cranial neuropathies, most commonly diplopia. Eighteen patients (78%) had findings referable to the spinal cord

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Initial Neurologic Symptoms</th>
<th>Neurologic Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Confusion</td>
<td>Altered mental state</td>
</tr>
<tr>
<td>2</td>
<td>Headache, nausea, ataxia</td>
<td>R LE paresis</td>
</tr>
<tr>
<td>3</td>
<td>Diplopia</td>
<td>CN VI palsy</td>
</tr>
<tr>
<td>4</td>
<td>Seizure</td>
<td>Hyporeflexia</td>
</tr>
<tr>
<td>5</td>
<td>Headache, nausea, LE numbness</td>
<td>Sensory level (T8), hyporeflexia, CN XXII palsies</td>
</tr>
<tr>
<td>6</td>
<td>Facial numbness/paresthesia</td>
<td>Hypoesthesia over chin</td>
</tr>
<tr>
<td>7</td>
<td>Headaches, blurred vision, weakness</td>
<td>Dysphasia, hyporeflexia, L Babinski sign</td>
</tr>
<tr>
<td>8</td>
<td>Nausea, facial paresthesia</td>
<td>NF</td>
</tr>
<tr>
<td>9</td>
<td>LE weakness/numbness</td>
<td>Paraparesis, hypoesthesia L2/L3 dermatomes bilaterally</td>
</tr>
<tr>
<td>10</td>
<td>Diplopia, paraparesis</td>
<td>NF</td>
</tr>
<tr>
<td>11</td>
<td>Headache, nausea, facial pain</td>
<td>L CN III, IV, VI, and VII palsy; hyporeflexia; Babinski sign</td>
</tr>
<tr>
<td>12</td>
<td>LE weakness and pain</td>
<td>Paraparesis</td>
</tr>
<tr>
<td>13</td>
<td>LE weakness/numbness, headache</td>
<td>Quadraparesis; LE areflexia</td>
</tr>
<tr>
<td>14</td>
<td>Global weakness, vision loss, confusion</td>
<td>Quadraparesis, Babinski signs, areflexia, LE hypостhesia</td>
</tr>
<tr>
<td>15</td>
<td>R LE weakness, confusion</td>
<td>Altered mental state; monoparesis; CN VI, VII, IX, X palsies</td>
</tr>
<tr>
<td>16</td>
<td>Headache, nausea, ataxia</td>
<td>Papilledema, CN III/V palsies, monoparesis, hyporeflexia</td>
</tr>
<tr>
<td>17</td>
<td>R UE weakness, LE numbness, Lhermitte sign</td>
<td>R UE monoparesis, hyporeflexia</td>
</tr>
<tr>
<td>18</td>
<td>Confusion</td>
<td>NF</td>
</tr>
<tr>
<td>19</td>
<td>Paraparesis, facial incontinence</td>
<td>NF</td>
</tr>
<tr>
<td>20</td>
<td>Sudden blindness, facial hypesthesia</td>
<td>Papillitis, areflexia, Babinski sign, monoparesis</td>
</tr>
<tr>
<td>21</td>
<td>Confusion, lethargy</td>
<td>Altered mental state</td>
</tr>
<tr>
<td>22</td>
<td>Diplopia, confusion, L LE weakness</td>
<td>R CN III palsy, L LE paresis, altered mental state, areflexia</td>
</tr>
<tr>
<td>23</td>
<td>Confusion, seizure</td>
<td>Altered mental state, L hemiparesis, areflexia</td>
</tr>
</tbody>
</table>

Abbreviations: CN, cranial nerves; L, left; LE, lower extremity; NF, no good documentation of the neurologic examination was found; R, right; UE, upper extremity.
or spinal nerve roots, with variations of extremity weakness, sensory disturbances, and abnormal myotatic stretch reflexes.

Twenty-one patients continued to receive care at our institution. During the course of their illness, many developed additional neurologic signs and symptoms. Ten patients (48%) developed new cerebral findings, 9 (43%) developed cranial nerve findings, and 5 (24%) developed spinal cord and nerve root findings. The cumulative account of their neurologic symptoms and signs included 21 (100%) with cerebral manifestations, 17 (81%) with cranial nerve manifestations, and 19 (91%) with spinal manifestations.

CSF FINDINGS

In 1 instance, no CSF results, other than positive cytoplogic findings, were found. The CSF from the remaining samples revealed either pleocytosis (median, 41 white blood cells per microliter; range, 1-790) or increased protein content (median, 196 g/dL; range, 24-838) in all but 1. Fifteen (68%) had more than 10 white blood cells per microliter, and plasma cells accounted for 50% or more of white blood cells in 14 patients. Of the 20 CSF samples that had protein measurements, 17 (85%) had elevated values, and in 14 (70%), the protein content was higher than 100 g/dL. Hypoglycorrhachia, defined as values below 2.8 mmol/L, was observed in 5 (26%) of 19 instances. The opening pressure was greater than 200 mm of water in 2 of the 5 cases in which it was measured. In all but 2 patients, the diagnosis of LMM was made on the first CSF examination. One patient was diagnosed on the second and 1 on the third CSF examination.

IMAGING

All patients had head magnetic resonance imaging with and without contrast, and 18 had spine magnetic resonance imaging (12 with contrast). Specific findings of CNS invasion included cranial leptomeningeal contrast enhancement in 16 (70%), either in a diffuse or focal pattern (Figure 2); spinal leptomeningeal contrast enhancement in 8, all with concurrent cranial meningeal enhancement (Figure 3); and leptomeningeal-based mass lesions in 4 patients (3 in brain and 1 in cord) (Figure 4 and Figure 5). One patient had a unilateral large subdural collection over the cerebral convexity that was initially misinterpreted as subdural hematoma but was found to be a malignant effusion at evacuation (Figure 6).

OUTCOME

At diagnosis of LMM, intrathecal chemotherapy was given once or twice weekly to all but 1 patient (who died 1 week after diagnosis). The dose of intrathecal chemotherapy was 12 mg of methotrexate or 30 mg of cytosine arabinoside plus 50 mg of hydrocortisone. Ommaya reservoirs were placed in 10 of 22 patients to ensure the in-
Figure 3. Spinal leptomeningeal contrast enhancement in leptomeningeal myelomatosis. A and B, T1-weighted postcontrast magnetic resonance images show thin leptomeningeal enhancement (arrows). C, Thick, nodular leptomeningeal enhancement (arrows). D and E, T2-weighted images show intradural, extramedullary nodules (arrows), causing displacement and edema of the spinal cord (arrowhead).

Figure 4. Leptomeningeal nodules in leptomeningeal myelomatosis simulating intraparenchymal lesions. A, T1-weighted postcontrast images show enhancing nodule at the medial surface of the left temporal lobe (arrow). B, Multiple contrast-enhancing intradural, extramedullary nodules (arrow) on the surface of the cord. The largest lesion (arrowheads) simulated an intramedullary lesion but was found to be extramedullary on axial images.
trathecal delivery of chemotherapy, which cannot be guaranteed by repeated spinal taps. The number of intrathecal treatments ranged from 3 to 12 depending on the clinical neurologic response, the overall clinical condition, and whether CSF sterilization was achieved. In addition, cranial radiation was given to 5 and craniospinal radiation to 7 patients who were judged to have clinically important nodular lesions.

Systemic treatment was administered to 18 patients. This consisted of intermediate-dose chemotherapy (5); salvage chemotherapy followed by allogeneic stem cell transplant (3); high-dose chemotherapy with autologous stem cell transplant (6); high-dose chemotherapy with autologous stem cell transplant followed by allogeneic stem cell transplant (2); and high-dose chemotherapy with allogeneic stem cell transplant (2). The 5 patients who did not receive systemic chemotherapy either died soon after diagnosis of LMM or refused further treatment.

Cytologic sterilization of CSF was achieved in 11 patients, 4 with and 7 without Ommaya reservoirs. The small

![Figure 5. Meningeal-based lesion simulating intraparenchymal plasmacytoma in leptomeningeal myelomatosis. Preoperative computed tomographic (A) and magnetic resonance (B-D) images in a patient who had seizures and was eventually found to have plasmacytoma. A. Dense mass lesion (arrow) and adjacent edema of the frontal and temporal lobes (arrowhead). B. Intense enhancement of the frontal lobe lesion (arrow) with thick meningeal enhancement (arrowhead). C. Intense lesion enhancement with evident leptomeningeal base (arrowhead). Thick meningeal enhancement (arrow) is again noted. D. Unilateral diffuse meningeal enhancement (arrows).](https://jamanetwork.com/)

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number of patients precludes statistical analysis concerning the superiority of intrathecal therapy via Ommaya reservoir over repeated taps. The median survival from diagnosis of LMM was 3 months (range, 0.1-25).

Postmortem examination was performed in 2 patients. Both had evidence of extramedullary disease in addition to involvement of the leptomeninges. Neither had evidence of intraparenchymal brain lesions.

**COMMENT**

We describe 23 patients with LMM encountered over the past 13 years at our institution from approximately 2000 patients with MM, for a prevalence of 1.1%. This is the largest series of patients with LMM, given that the relevant literature consists of case reports (approximately 70 patients). There are several possible explanations for the accumulation of this large experience. First, numerous patients with MM are referred to our institution. Second, a considerable proportion of these patients have biologically aggressive disease. Fassas et al found a strong association between LMM and biological markers of aggressive MM. Another possible explanation is the prolongation of MM survival achieved by high-dose chemotherapy and stem cell support. Higher prevalence of leptomeningeal cancer was observed in patients with breast and lung cancer following treatment-induced prolonged survival. However, the relatively short interval between diagnoses of MM and LMM, not appreciably longer than the median survival achieved with conventional chemotherapy (24-36 months), argues against the view that this mere prolongation of survival might lead to higher prevalence of LMM; it supports the contention that the inherent biological features of the disease are primarily responsible for LMM.

The prevalence of 1.1% of LMM in patients with MM is much lower than that reported in other hematologic malignancies, with rates of up to 75% in acute lymphocytic leukemia and 25% in diffuse histiocytic and undifferentiated pleomorphic lymphomas. Even in solid tumors, the prevalence of leptomeningeal metastases is higher, with 2% to 5% in breast cancer and 26% in small-cell lung cancer. The reasons underlying the relative paucity of CNS invasion by MM in comparison with other tumors, whether solid or hematological, remain unknown, but this phenomenon might be the result of underlying biological characteristics, or lack thereof, of malignant plasma cells.

In this series, there were no distinct neurologic symptoms or signs that were specific to the clinical diagnosis of LMM. Most of our patients had symptoms and signs referable to more than 1 neurologic axis, similar to the experience in other leptomeningeal malignancies. Diagnostic imaging findings with comparable sensitivity of leptomeningeal enhancement by magnetic resonance imaging.

Cerebrospinal fluid examination remains the definitive test for diagnosing LMM. In addition to positive cytologic findings, CSF studies showed either pleocytosis or increased protein in all but 1 patient. The same is true regarding diagnostic imaging findings with comparable sensitivity of leptomeningeal enhancement by magnetic resonance imaging.

The prognosis of patients with LMM is poor, despite aggressive local and systemic treatment. Even when sterilization of CSF was achieved, patients' survival was limited by the aggressive systemic disease. We frequently detected high-risk cytogenetic abnormalities in both bone marrow and CSF: plasmablastic morphology, extramedullary manifestations, plasma cell leukemia, and high serum lactate dehydrogenase levels were commonly found in our patients. These are characteristics of aggressive myeloma with genetic drug resistance and growth potential independent of the bone marrow microenvironment, and they are predictors for poor survival.

**Figure 6.** Subdural malignant effusion mimicking subdural hematoma. A, Precontrast computed tomography showing hyperdense, subdural mass consistent with subdural hematoma (arrows). B, T2-weighted magnetic resonance imaging showing thick subdural mass (arrows). C, The lack of enhancement on T1-weighted image (arrows), unusual for malignant lesions, led to the preoperative misdiagnosis of chronic subdural hematoma.
Almost all of our patients with LMM had evidence of extensive systemic disease. It is our belief the isolated CNS relapses, which are rare and inadequately documented, represent the current inability to document low-volume systemic MM. Thus, leptomeningeal seeding is a concomitant of aggressive MM rather than a sign of progression to more advanced disease.

Despite that, we believe that treatment of LMM is indicated, given its potential for symptomatic relief and improvement in the quality of life. Physicians should be alert to the possibility of LMM given its serious prognostic implications. Better understanding of the biology of LMM may allow prospective and earlier recognition and treatment of patients at risk for this complication.

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Previous Presentation: This study was presented in part at 2003 annual meeting of the American Academy of Neurology.

REFERENCES