

Multiple Myeloma Invasion of the Central Nervous System

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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.

Arch Neurol. 2004;61:1423-1429

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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.¹ While infiltration of the leptomeninges by various malignancies is well known,² invasion of the central nervous system (CNS) in MM is rare, either as presumed intracerebral metastases^{3,4} or as leptomeningeal myelomatosis (LMM),⁴⁻¹² 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.^{13,14} 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 patients¹⁵ and an invited review¹⁶ 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 subse-

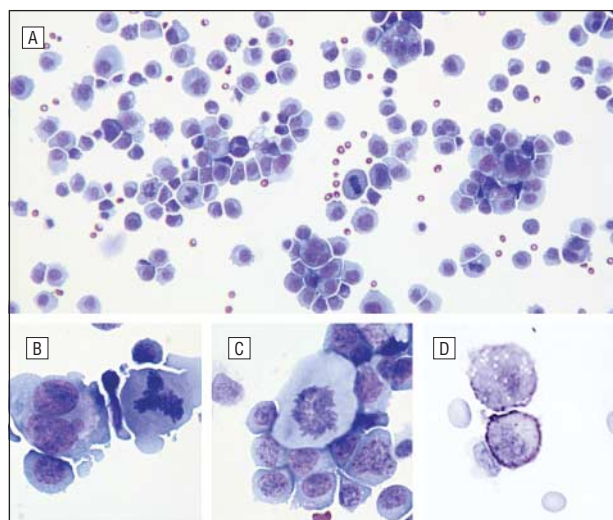


Figure 1. Cerebrospinal fluid cytologic findings in leptomeningeal myelomatosis. A, Low-power view of pleomorphic plasma cells, often clumped, and few erythrocytes. B and C, Higher-power view of multinucleated myeloma cell and others undergoing mitosis. D, Immunohistochemical stain for syndecan-1 showing monoclonality.

quent 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

Neurologic Symptoms and Signs in Patients With Leptomeningeal Myelomatosis

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

Abbreviations: CN, cranial nerves; L, left; LE, lower extremity; NF, no good documentation of the neurologic examination was found; R, right; UE, upper extremity.

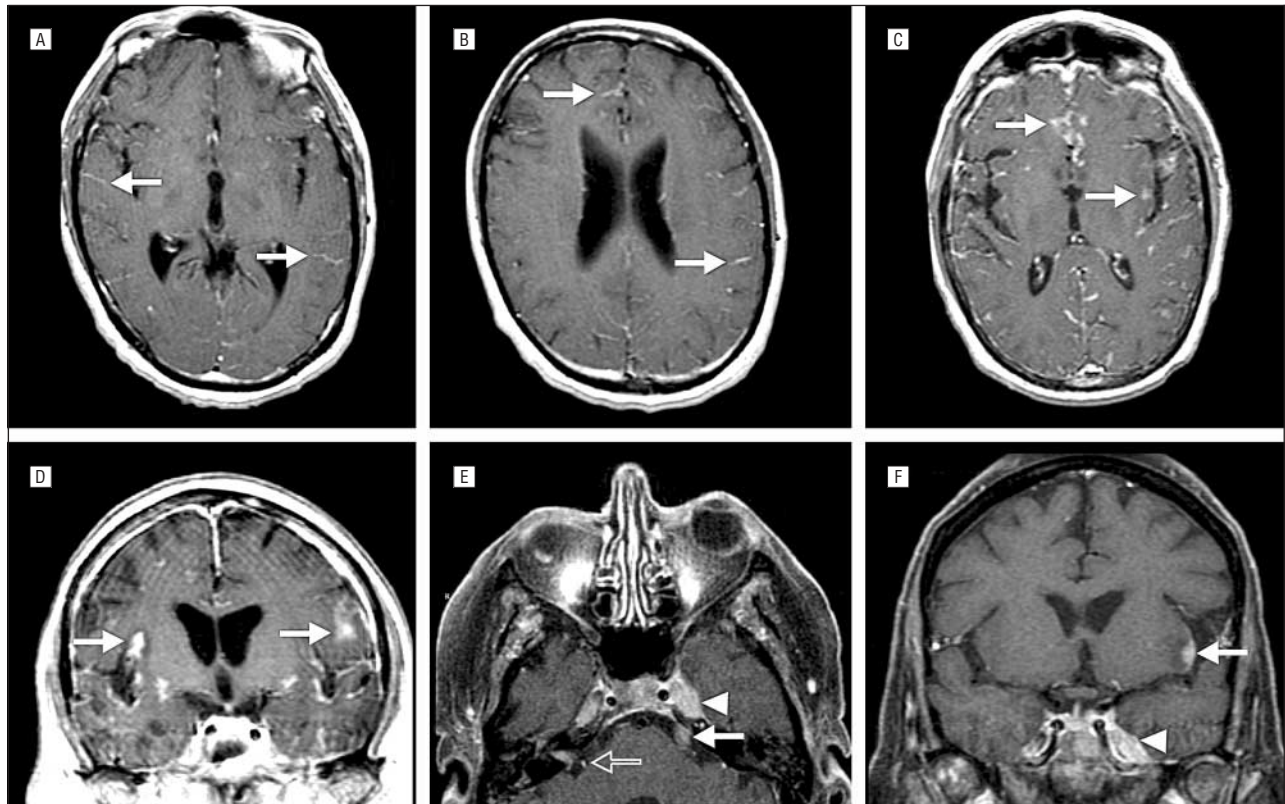


Figure 2. Cranial leptomenigeal contrast enhancement in leptomenigeal myelomatosis. A and B, T1-weighted, postcontrast magnetic resonance images show thin, linear leptomenigeal enhancement (arrows). C and D, Diffuse, thick, irregular leptomenigeal enhancement (arrows). E, T1-weighted postcontrast fat-suppressed images show nodular areas of enhancement along the base of the brain, with enhancement of the left cavernous sinus (arrowhead), left fifth (arrow), and right seventh and eighth cranial nerves (open arrow). F, Nodular area of enhancement along the left insula (arrow) and of the left cavernous sinus (arrowhead).

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 cytologic 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 leptomenigeal contrast enhancement in 16 (70%), either in a diffuse or focal pattern (**Figure 2**); spinal leptomenigeal contrast enhancement in 8, all with concurrent cranial meningeal enhancement (**Figure 3**); and leptomenigeal-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-

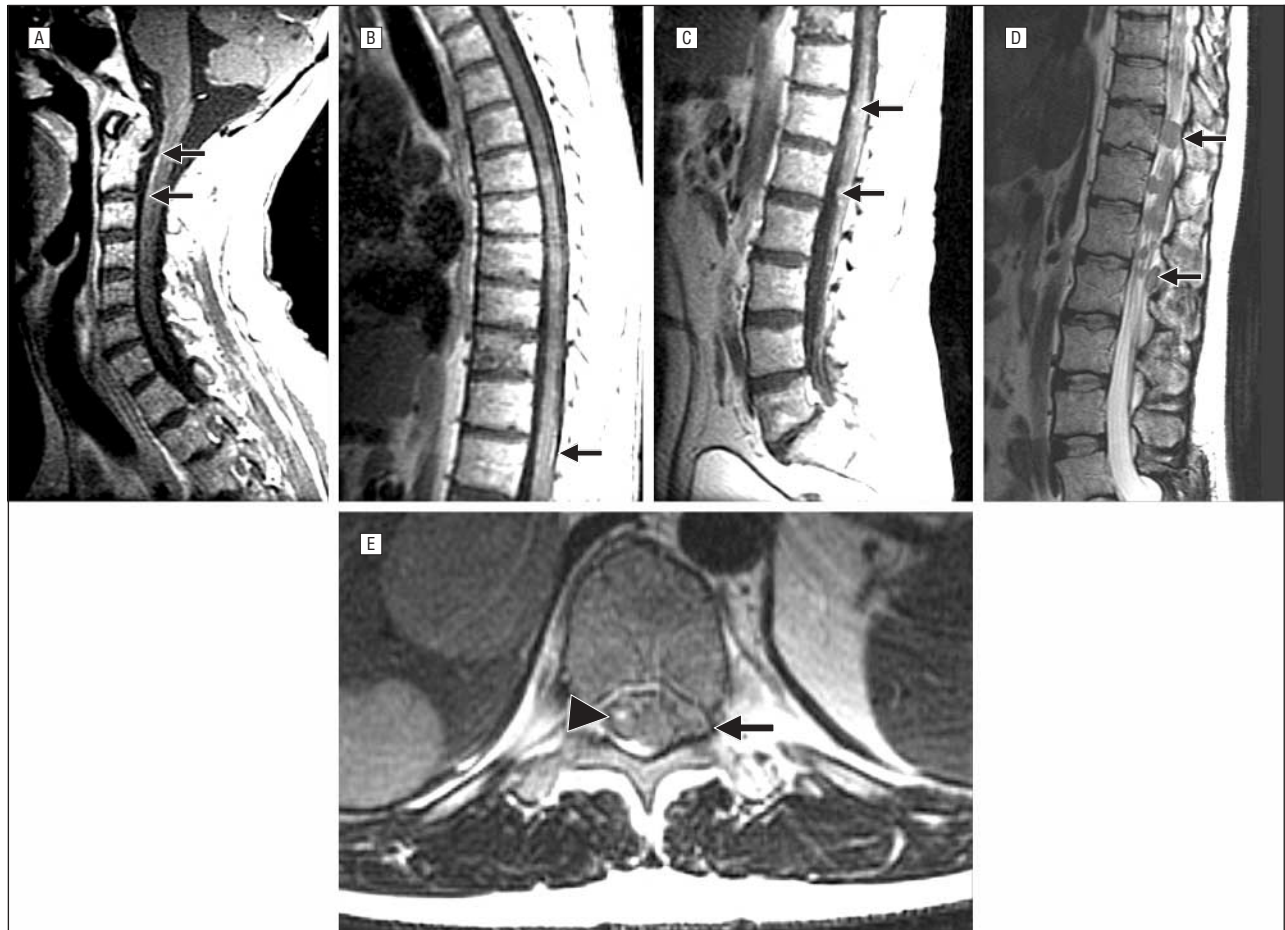


Figure 3. Spinal leptomenigeal contrast enhancement in leptomenigeal myelomatosis. A and B, T1-weighted postcontrast magnetic resonance images show thin leptomenigeal enhancement (arrows). C, Thick, nodular leptomenigeal enhancement (arrows). D and E, T2-weighted images show intradural, extramedullary nodules (arrows), causing displacement and edema of the spinal cord (arrowhead).

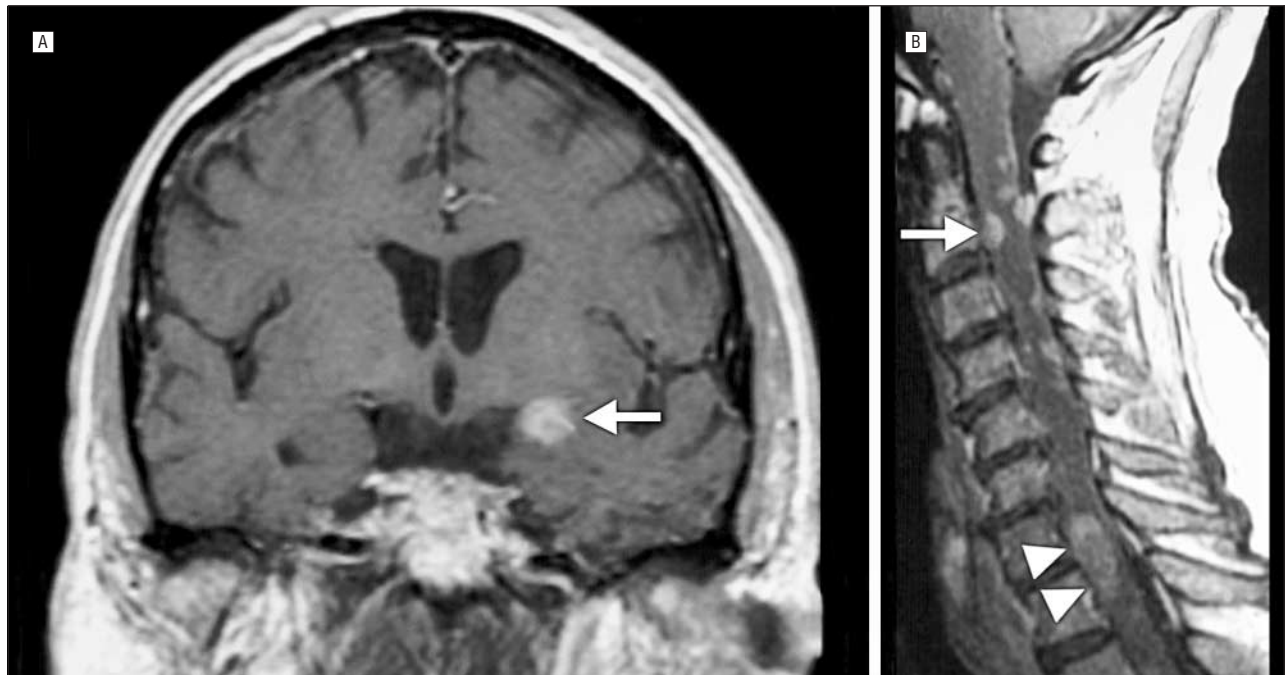


Figure 4. Leptomenigeal nodules in leptomenigeal myelomatosis simulating intraparenchymal lesions. A, T1-weighted postcontrast images show enhancing nodule at the medial surface of the left temporal lobe (arrow). B, Multiple contrast-enhancing intradural, extramedullary nodules (arrow) on the surface of the cord. The largest lesion (arrowheads) simulated an intramedullary lesion but was found to be extramedullary on axial images.

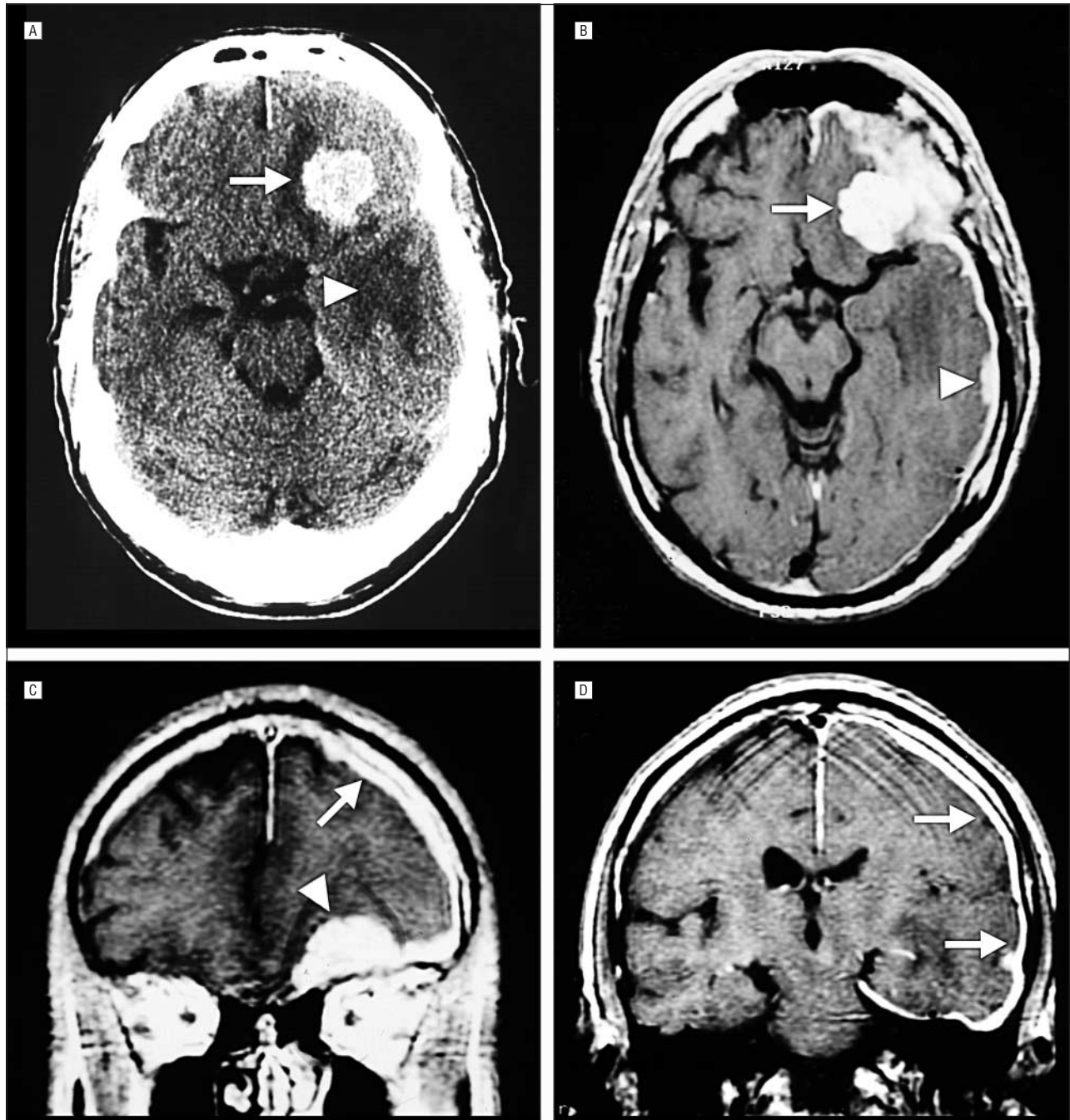


Figure 5. Meningeal-based lesion simulating intraparenchymal plasmacytoma in leptomenigeal myelomatosis. Preoperative computed tomographic (A) and magnetic resonance (B-D) images in a patient who had seizures and was eventually found to have plasmacytoma. A, Dense mass lesion (arrow) and adjacent edema 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 leptomenigeal base (arrowhead). Thick meningeal enhancement (arrow) is again noted. D, Unilateral diffuse meningeal enhancement (arrows).

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); sal-

vage 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

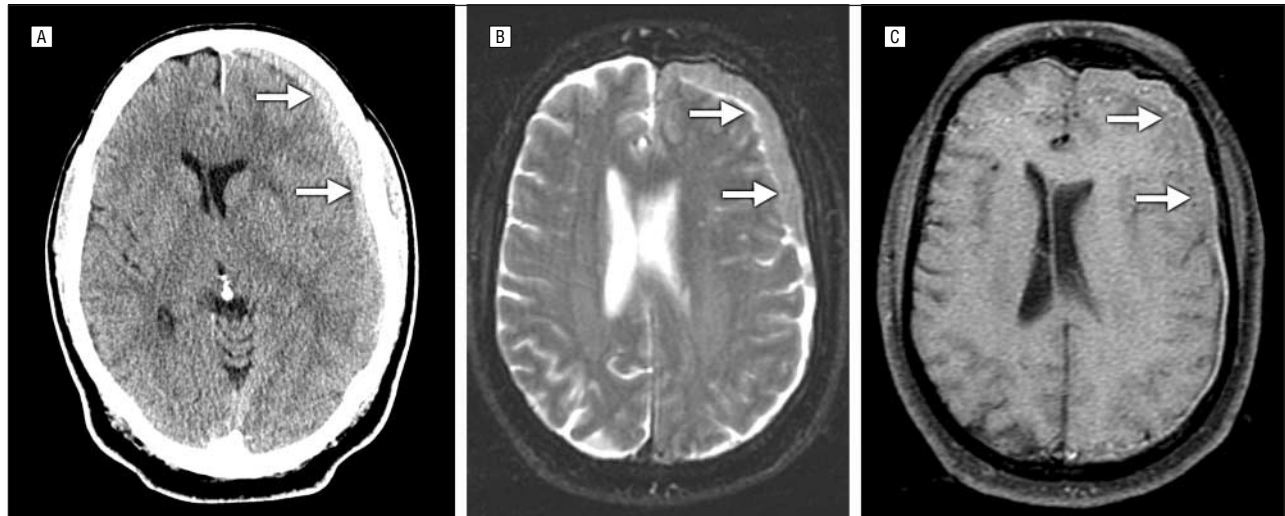


Figure 6. Subdural malignant effusion mimicking subdural hematoma. A, Precontrast computed tomography showing hyperdense, subdural mass consistent with subdural hematoma (arrows). B, T2-weighted magnetic resonance imaging showing thick subdural mass (arrows). C, The lack of enhancement on T1-weighted image (arrows), unusual for malignant lesions, led to the preoperative misdiagnosis of chronic subdural hematoma.

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 al¹⁵ 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.^{13,14} Higher prevalence of leptomeningeal cancer was observed in patients with breast and lung cancer following treatment-induced prolonged survival.^{17,18} 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.^{19,20} Even in solid tu-

mors, the prevalence of leptomeningeal metastases is higher, with 2% to 5% in breast cancer¹⁸ and 26% in small-cell lung cancer.¹⁷ 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.²¹ The same is true regarding diagnostic imaging findings with comparable sensitivity of leptomeningeal enhancement by magnetic resonance imaging.²⁰

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. In other leptomeningeal cancers, serial CSF examinations are frequently required for diagnosis. In our patients, the diagnosis was established on the first examination in all but 2 patients. We speculate that malignant myeloma cells are less adherent to tissues and easier to detect on CSF cytologic findings than other solid tumors. We have not systematically measured immunoglobulin levels in CSF samples and therefore cannot comment on the utility of CSF immunofixation for diagnosis of LMM.

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.¹⁵ 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.

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.

Accepted for Publication: February 26, 2004.

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

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