Original Study

Myelomatous Involvement of the Central Nervous System

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Abstract

Myelomatous involvement of the central nervous system (CNS) is an uncommon complication that portends a poor prognosis in patients with multiple myeloma (MM). Limited data exist regarding the optimal management of CNS MM. In the present case-control study, we examined the clinical presentation, diagnosis, treatment, and outcomes of CNS MM patients compared with a control group of MM patients without CNS involvement, matched by date of diagnosis and gender.

Introduction: Limited data exist with respect to the outcome and optimal treatment of patients with myelomatous involvement of the central nervous system (CNS). **Materials and Methods:** Of 4060 patients with multiple myeloma (MM), evaluated at Mayo Clinic from 1998 to 2014, 29 (0.7%) had identifiable CNS involvement, established by the presence of atypical plasma cells in the cerebrospinal fluid (CSF) and/or identification of intraparenchymal or meningeal involvement on magnetic resonance imaging (MRI). A cohort of 87 MM patients without CNS disease served as the control group (1:3), matched by diagnosis date and gender. **Results:** Plasma cells were detected in the CSF in 87% and MRI findings consistent with CNS involvement were noted in 82% of the patients. A bone marrow plasma cell labeling index of $\geq$ 3%, the presence of disease at other extramedullary sites, or peripheral blood plasma cells of $>$ 800 per 150,000 events were associated with an odds ratio of 7.1, 10.3, and 14, respectively, for the risk of CNS involvement. Overall survival (OS) from the diagnosis of MM was significantly shorter in the CNS-MM group (median 40 months; 95% confidence interval [CI], 24-56 months) than in the control group (median, 93 months; 95% CI, 67-129 months). OS was 3.4 months from the detection of CNS disease. Patients who underwent autologous stem cell transplantation after CNS involvement (n = 7) had a median OS of 19 months (95% CI, 10-67 months) from the detection of CNS involvement. **Conclusion:** Myelomatous involvement of the CNS is a rare complication that portends a poor survival. Current therapeutic approaches appear to be largely ineffective for this subset of patients with MM.

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Introduction

Multiple myeloma (MM) is characterized by the clonal proliferation of plasma cells producing monoclonal immunoglobulin. The clonal plasma cell in MM is primarily confined to the bone marrow and vascular compartments; however, extramedullary organ involvement is evident in 7% to 20% of patients with MM.[1,2] The risk of involvement of the central nervous system (CNS) is estimated to be approximately 1% in patients with established MM,[3] with overall survival (OS) reportedly $<$ 6 months from the detection of CNS disease.[4,5]

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Improvement in OS from the diagnosis of MM appears to be contemporaneous with the increasing use of novel agents such as bortezomib, lenalidomide, and thalidomide.[6,7] One study, however, suggested that the rate of CNS MM has increased since the integration of novel anti-MM agents into the treatment armamentarium.[8] This observation was perceived to be related, in part, to the evolution of the plasma cell clone to be able to survive and expand outside the bone marrow environment, tumor microenvironmental changes leading to inhospitable marrow milieu for the myeloma cells, and the limited penetrability of the blood–brain barrier (BBB) by most of the approved anti-MM therapies.

The paucity of clinical data from patients with CNS myeloma has led to a lack of clarity with respect to the clinical and laboratory features that can reliably identify patients at the initial presentation with an increased risk of developing myelomatous involvement of the CNS. In the present study, we compared a cohort of MM patients with CNS involvement with a control population of patients without CNS involvement to discern the unique clinical features associated with CNS MM; determine the factors predisposing a patient to CNS involvement; assess the natural history of patients from the detection of CNS disease; and explore the optimal management strategies for this rare complication.

Materials and Methods

The electronic medical records of all patients with a diagnosis of MM who were evaluated at Mayo Clinic (Rochester, MN) from January 1, 1998 to December 31, 2014 were queried using the advanced cohort explorer search tool for any evidence of myelomatous CNS disease using the diagnosis and procedure codes for multiple myeloma, lumbar puncture, and magnetic resonance imaging (MRI) and the keywords atypical plasma cells, leptomeningeal enhancement, and intraparenchymal/cerebral/brain lesions. CNS involvement was established by the presence of atypical plasma cells in the cerebrospinal fluid (CSF) and/or radiographic identification of intraparenchymal lesions or leptomeningeal enhancement or direct tissue sampling.

The MRI findings were categorized as intraparenchymal plasmacytomas (presence of characteristic single or multiple parenchymal lesions without any evidence of a nonmyelomatous primary malignancy); myeloma-related leptomeningeal disease (significant enhancement of the meninges); and dural disease or direct extension into the CNS (skull or vertebral myelomatous lesions penetrating through the meninges at least to the subdural space with or without dural enhancement). Patients with plasmacytomas in contact with, but without associated meningeal enhancement, were not classified as having CNS MM. Patients with isolated spinal cord compression from pathologic fractures without other signs of meningeal enhancement were also excluded. A flow cytometric analysis of the CSF suspected of harboring malignant plasma cells was performed using monoclonal antibodies to CD19, CD38, CD45, CD138, and cytoplasmic kappa and lambda light chains.

The cases were defined as patients in whom CNS myeloma was detected either at the diagnosis of MM (primary CNS involvement) or in the relapsed setting during follow-up (secondary CNS involvement). The controls were defined as patients with a diagnosis of MM but without any symptoms to raise the suspicion of myelomatous CNS involvement at diagnosis or during the follow-up period. For each case, 3 controls were selected from a large cohort of patients with active MM seen at our institution and matched by gender and date of MM diagnosis. Once the controls were identified, their electronic medical records were also reviewed, and information pertaining to demographic data, clinicopathologic data, therapy administered, and follow-up data was retrieved.

Patients with any of the following high-risk features [fluorescence in situ hybridization (FISH), deletion 17p, t(4;14), t(14:16), t(14:20); deletion 13 or hypodiploidy found on cytogenetic examination; plasma cell labeling index (PCLI) $\geq$ 3% or plasma cell leukemia] were included in the high-risk group, and the remainder were included in the standard-risk group.[9] The PCLI was measured using either the slide-based immunofluorescence method or flow cytometry to assess the proliferation capacity of plasma cells through staining of double-stranded DNA.[10] Flow cytometry was used to assess the presence of circulating plasma cells in the peripheral blood. Mononuclear cells isolated by Ficoll gradient from patients' peripheral blood samples were stained with antibodies to CD19, CD38, CD45, and CD138 and cytoplasmic kappa and lambda light chains. Circulating plasma cells were detected using a 6-color multiparameter flow cytometer (BD FACS Cantos II instruments; Becton Dickinson, Franklin Lakes, NJ) with the aim of analyzing data from 150,000 cellular events per patient using BD FACS Diva software (Becton Dickinson). The clonal circulating plasma cells were characterized by an abnormal phenotype lacking CD19 expression but variably expressing CD45. Cytoplasmic immunoglobulin light chain restriction (kappa/lambda expression ratio of either $>$ 4:1 [kappa restricted] or $<$ 1:2 [lambda restricted]) was used to confirm clonality, with final results reported as the number of clonal plasma cells per 150,000 events.

The date of diagnosis of MM and the date of detection of CNS involvement was used for all time-to-event analyses. OS was estimated using the Kaplan-Meier method.[11] Continuous variables were summarized as the median and standard deviation. Fisher's exact test was used to compare the cases and controls. Conditional logistic regression models were used to estimate the odds ratios (ORs) and the associated 95% confidence intervals (CIs). For patients with circulating plasma cells, a receiver operating characteristic analysis was performed to determine the optimal cutoff point for the circulating plasma cells to predict subsequent or concurrent involvement of the CNS. For all tests, $P < .05$ was considered statistically significant. All analyses were performed using JMP, version 10.0, software (SAS Institute Inc, Cary, NC). All procedures were followed in accordance with the ethical standards of the institutional review board and the Declaration of Helsinki.

Results

Patient Characteristics

Myelomatous involvement of the CNS was identified in 29 of 4060 patients (0.7%) with MM from 1998 to 2014. Of the 29 patients, 7 (24%) had CNS involvement at the diagnosis of MM (primary CNS MM) and 22 had CNS disease detected in the relapsed or refractory stage. Most patients (72%) were diagnosed with CNS disease after 2005; however, the rate of CNS involvement was similar before (0.5%) and after (0.7%) 2005. The median age at the diagnosis of CNS myeloma was 59 years (range, 37-80 years), and 72% of the patients were men. CNS involvement was