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Leptomeningeal Myelomatosis: An Unusual Presentation of Multiple Myeloma

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Abstract

Multiple myeloma (MM) is characterized by the neoplastic proliferation of plasma cells producing a monoclonal immunoglobulin. Although neurological complications are commonly seen in MM, they most frequently occur due to spinal cord compression by bony lesions, paraprotein-related neuropathy, hypercalcemia, hyper viscosity, or amyloidosis. Less than 1% of patients with MM present with a leptomeningeal disease. We present a case of a leptomeningeal myeloma in a 61-year-old woman with known relapsed MM who presented with headaches and dysphagia. We present this case to alert clinicians to keep a high index of suspicion in cases of Multiple Myeloma presenting with non-specific neurological symptoms.

Introduction

Case Report

A 61-year-old white female who was extremely healthy and had no major health issues presented with left hip and bilateral rib pain. The initial physical examination was significant for bilateral axillary adenopathy. Her initial labs showed that her CBC and CMP were within normal limits. Free light chain analysis showed serum kappa light chains at 1048, and serum lambda light chains normal at 10. Serum protein electrophoresis showed an M protein of 1.8 and immunofixation confirmed IgA kappa. MRI of the hip showed multifocal areas of abnormal marrow signal most pronounced in the left superior pubic ramus extending with some cortical breakthrough and periosteal edema. Bone marrow biopsy revealed hypercellular marrow with atypical plasma cell infiltrates of 20% with kappa light chain restriction and surface marker positive for CD 56. Furthermore, karyotyping showed abnormal complex karyotypes with unbalanced rearrangement resulting in gain of 1q, monosomy 13, rearrangement of 14q, all consistent with high-risk myeloma.

The axillary lymph node biopsy confirmed the presence of a plasmacytoma with kappa light chain restriction and surface marker positive for CD 56. She was confirmed to have stage III Multiple Myeloma with high-risk features. She was treated with the induction therapy of RVD (Lenalidomide, Bortezomib, and Dexamethasone), a standard and typically highly effective course of treatment. She completed six cycles of RVD with complete remission. At that time, she was advised of her options. Due to her high risk features it was advised that she undergo high dose chemotherapy with autologous Peripheral blood stem cell transplant (PBSCT). However, she declined an autologous PBSCT and was placed on maintenance Lenalidomide.

Eleven months following her remission, she saw an ear nose and throat (ENT) physician for acute onset of nausea, vomiting, dysphagia and dysarthria. ENT evaluation showed a paralyzed left vocal cord. MRI of the brain at that time was interpreted as unremarkable. CT Chest did not show any lesions to explain her symptoms. Barium swallow was unremarkable. Speech therapy provided no improvement. Her symptoms worsened with additional development of bladder and bowel incontinence, twenty-pound weight loss and paraparesis. PET-CT scan showed progression of bone metastases and recurrence of hypermetabolic right axillary adenopathy. A Biopsy of right axilla confirmed recurrent Multiple Myeloma. Due to the nature of the disease progression, repeat MRI of the Brain at a tertiary care center confirmed extensive leptomeningeal disease involving the posterior fossa and supratentorial brain and ventricular system. Cerebrospinal fluid analysis confirmed the presence of malignant plasma cells. Her overall prognosis was deemed very poor and hospice care was advised. She initially declined hospice and was briefly given one cycle of Carfilzomib and dexamethasone which she tolerated poorly. She was deemed too sick for Intra-thecal chemotherapy. She was admitted to the hospital for dehydration, pneumonia, and a Stage 4 sacral decubitus ulcer. She Passed away Under Hospice Care.

Discussion

Multiple Myeloma involvement of the Central Nervous System (CNS) is rare and is seen in less than 1% of MM patients [1]. As seen in our case report, the presenting symptoms can be non-specific. They can present with a variety of symptoms ranging from nausea, vomiting, swallowing and speech difficulty, mental status changes, gait disturbances, visual disturbanc-

es to cranial nerve palsies. CNS involvement of Myeloma can be classified into four groups based on a review by Dispenzieri and Kyle:(a) those extending from the skull pressing inward, (b) those growing from the dura mater or the leptomeninges, (c) those arising from the mucous membranes of a nasopharyngeal plasmacytoma, and (d) intraparenchymal lesions without evidence of extension from any of these other three sites [2]. Leptomeningeal involvement has the worst prognosis with the median survival ranging from 1.5- 3 months [3-6].

Pathogenesis

The exact pathogenesis of MM remains unknown. The most common CNS manifestation is involvement of dura. This Dural involvement occurs due to direct extension of a plasmacytoma of the skull into the CNS [7]. It is likely that hematogenous spread of plasma cells occurs in CNS MM. The other theory is that CNS involvement results from the evolution of aggressive clones of plasma cells, as most drugs used in MM cannot cross the blood- brain barrier [1].

Risk factors

As evidenced from our case, several high-risk factors have been identified in CNS involvement by MM. Deletions of chromosome 17p13.1 (p53) have been found in 89% of the CNS MM patients [8]. Other risk factors include extra-medullary MM, plasmablastic morphology, cytogenetic abnormalities, high tumor load, increased LDH levels, circulating plasma cells [9]. Our patient had evidence of a high myeloma burden, stage III disease (by Dure- Salmon and ISS staging systems), extra-medullary MM, IgG kappa MM and the presence of a paraspinal plasmacytoma. Fluorescence in situ hybridization (FISH) analysis did not show any evidence of IGH-FGFR3 fusion product or proof of an aberration involving chromosome 17p. An unbalanced chromosome 1q gain was identified, which has been associated with an adverse prognosis in some studies. This patient would be considered at high risk of developing CNS MM, based on the research available.

Treatment

No effective treatments exist for CNS MM. This is also reflective of the fact that these tend to be high risk patients with aggressive disease based on genetic profiles where the treatments are less effective. Usually, active drugs in MM such as the proteasome inhibitors (bortezomib, carfilzomib, and ixazomib), cannot cross the blood-brain barrier, and standard chemotherapy drugs used to treat CNS lymphoma and brain cancer are not particularly effective in MM. Although the IMiDs (thalidomide, lenalidomide, and pomalidomide) do cross the blood-brain barrier; IMiD resistance is common in this group of patients. Several new drugs have not been studied in this groups of patients as CNS involvement were an exclusion criterion in the registration trials. It is unknown whether CD38 antibodies can get through the blood-brain barrier. NO data exists on the intrathecal use, of these new drugs. Retrospective data support the use of craniocaudal radiotherapy and possibly ASCT as consolidation [5].

Some limited data with new drugs in CNS MM is available. A case report showed efficacy of pomalidomide in CNS MM [12]. Pomalidomide is an IMiD which has been shown to be more effective in high-risk cytogenetics, especially deletion 17p, than other IMiDs and has good CNS penetration [13]. Another new drug that has shown to be potentially effective in CNS MM is marizomib, a potent natural second-generation proteasome inhibitor produced by a marine bacterium, which was used successfully in two cases of CNS MM [11]. Recent data also shows some benefit to Daratumumab in CNS disease. Craniospinal radiation has been shown to increase OS as has intrathecal chemotherapy in small series of selected patients [14-16]. Widespread application of these is limited by patient's poor performance score.

Conclusions

CNS MM is a very rare complication of MM that carries a poor prognosis with OS of approximately 3 months. A variety of treatment strategies have been adopted, but prognosis remains short, except in rare case reports.

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