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Central nervous system involvement in multiple myeloma.

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Abstract

Multiple myeloma (MM) is a monoclonal gammopathy known as the malignant proliferation of plasma cells presenting typical complications like hypercalcemia, osteolytic bone lesions, anemia, renal insufficiency, and infections. Central nervous system (CNS) involvement in multiple myeloma, also known as leptomeningeal myelomatosis is uncommon and has been reported only in 1% of patients. Represents a complication of multiple myeloma in which the pathophysiology of migration and proliferation of plasma cell remains unknown. The diagnosis hallmark for this entity is the presence of plasma cells in cerebrospinal fluid (CSF). The reduced number of patients with leptomeningeal myelomatosis makes unclear the optimal therapy for this condition. Intrathecal therapy has shown to be an effective therapy to clear plasma cells from CSF. We present a case of a 40-year-old patient with multiple myeloma and central nervous system involvement on his first relapse, treated with combined therapy.

KEYWORDS: multiple myeloma; central nervous system involvement

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Invasión al sistema nervioso central de mieloma múltiple

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Resumen

El mieloma múltiple es una gammapatía monoclonal con proliferación de células plasmáticas; se manifiesta con complicaciones típicas, como hipercalcemia, lesiones osteolíticas, anemia, insuficiencia renal e infecciones. La afectación del sistema nervioso central en el mieloma múltiple (mielomatosis leptomeníngea) no es común y se ha reportado sólo en 1% de los pacientes. El diagnóstico se establece con la identificación de células plasmáticas en el líquido cefalorraquídeo. Debido al número reducido de pacientes con mielomatosis leptomeníngea, no se ha definido un tratamiento óptimo. El tratamiento intratecal ha demostrado ser efectivo para eliminar las células plasmáticas del líquido cefalorraquídeo. Se comunica el caso de un paciente de 40 años con mieloma múltiple en su primera recaída con afectación del sistema nervioso central, al que se le prescribió tratamiento combinado.

PALABRAS CLAVE: mieloma múltiple, daño al sistema nervioso central.

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BACKGROUND

Multiple myeloma (MM) represents the prototype of a malignant monoclonal gammopathy. Manifestations occur by the tumoral proliferation of Immunoglobulin-secreting plasma cells, which are restricted to the bone marrow.[1-3] This proliferation may occur in a localized form or in a generalized form, in which MM is the most representing.[4]

Central nervous system (CNS) involvement in MM is a rare manifestation in this entity, representing 1% of patients;[5] CNS myelomatosis is determined by the presence of plasma cells in cerebroespinal fluid.[6]

Leptomeningeal myelomatosis is very uncommon and rarely detected in alive patients, but sometimes found at autopsy;[4] the process regarding the migration of plasma cells to the leptomeninges is uncertain.[2] We present a rare case of a patient with leptomeningeal myelomatosis who received two autologous hematopoietic stem cells transplantations (HSCT), and who is currently alive, in partial remission, after twenty months of the CNS MM diagnosis.

CASE REPORT

A 40-year-old man with previous diagnosis of multiple myeloma (MM) came to our center to be evaluated and treated. He was diagnosed with MM in October 2012 in another center, where he was treated with bortezomib and received an autologous stem cell transplant in September 2013, obtaining partial remission. He also presented secondary renal insufficiency. He was referred to our center in March 2014 after the development of external ocular motor palsy, diplopia, dyslalia, bone pain and recurrence of IgG and kappa chains elevation in serum. Urinalysis reported 0.25 proteins, heavy gamma chains, light kappa chains and monoclonal free kappa light chains. In the serum kappa and lambda chains were detected.

In the bone marrow aspirate morphology 3% of plasma cells were detected. In FISH method IgH/FGFR3 was analyzed; 100 cells were negative for t(4;14).

The cerebrospinal fluid (CSF) showed: total proteins 300 mg/dL (normal values 15-26 mg/dL), positive for globulins and 28% of plasma cells. CSF was also subjected to flow cytometric analysis, reporting plasma cells positive for CD19+/-, CD38+/-, CD38++, CD45+/- and CD56+, representing 30% of total cells. 13q-,and 17p deletion by FISH methods were negative; 17p deletion was positive in 3 of 100 cells analyzed.

Brain MRI reported subdural lesions probable compatible with plasmacytomas. After the complete analysis, CNS involvement with multiple myeloma was diagnosed.

We started the induction treatment with intensive chemotherapy (VDT-PACE) and weekly intrathecal chemotherapy (IT) obtaining an impressive clinical response, he fully recovered the speech and visual capacity. The cerebrospinal fluid was clear of plasma cells after the fourth weekly intrathecal chemotherapy. He continued maintenance treatment with weekly bortezomib, low dose lenalidomide and monthly intrathecal chemotherapy. A second autologus transplant was performed using our method on July 2015 with non-cryopreserved peripheral blood stem cells as consolidation treatment.[7]

DISCUSSION

CNS involvement is an uncommon complication of MM; the patient was diagnosed with MM and two years after he developed neurological symptoms caused by leptomeningeal myelomatosis. The first symptoms were external ocular

motor palsy, dyslalia and recurrence in IgG and kappa serum chains elevation. The craneal nerve III palsy described in this case is extremely uncommon and usually due to an intracraneal plasmacytoma.[8] In MM there is a modification in the DNA of Ig genes, caused by hypermutation and antigen selection inside plasma cells.[9] There are five heavy chain isotypes (M, G, A, D, E) and two light chain isotypes (Kappa, lambda); monoclonal proteins IgG and IgA are very common, Ig D and Ig E are rare and uncommon;[10] our patient presented heavy gamma chains; in serum kappa and lambda chains were detected with predominating light kappa chains.

Bone marrow aspirate revealed 3 percent of plasma cells; the urinalysis reported 0.25 proteins. CSF examination reported proteins, plasma cells and globulins thus confirmed CNS infiltration and suggested intracraneal plasmocytomas, only seen in 1% of all the patients with MM,[11] the plasma cells were positive for CD19+/-, CD38+/-, CD38++, CD45+/- and CD56+ (representing 30% of total cells) with a cellular population that expressed a characteristic inmunophenotype of neoplastic plasmatic cells.

MRI of the head showed extra-axial subdural lesions suggestive of plasmocytomas which confirmed the CNS involvement and relapse of previous MM. Considering all these facts and his first relapse, intensive chemotherapy was initiated with VDT-PACE (bortezomib, dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, etoposide) as induction before transplantation; this regimen reduces the disease burden in very aggressive MM resistant to conventional therapies.[12] The use of intensive chemotherapy combinations, can be effective salvage for refractory myeloma and can prevent further haematogenous extension into the CNS. The reduced number of patients with this complication (CNS involvement) makes unclear the optimal therapy for CNS myeloma. Most published reports to date describe dismal survival of 1-2 months with traditional approaches incorporating the use of IT chemotherapy and radiation. Repeated doses of intrathecal (IT) chemotherapy offers control of local CNS disease, clearing plasma cells from CSF, prolonged duration of local CNS disease control can be achieved with this treatment modality.[2] The use of radiotherapy for the treatment of CNS MM is frequently used and in some reports has been associated with longer survival but its definitive use should be further evaluated.[13] The VDT-PACE regimen and intensive IT chemotherapy combination can be effective for refractory myeloma,[2] such as the one described in this patient.

Bortezomib modulates the ubiquitin pathway, resulting in cytotoxic injury due to disruption or protein degradation. Immunomodulatory agents (IMIDs) such as thalidomide and lenalidomide improve several mechanisms (direct toxicity, activation of antitumor immunity and antiangiogenic effects) to target myeloma cells[14] and have the ability to cross de blood brain barrier.[2] The treatment with bortezomib and lenalidomide showed improvement in some cases but there is scanty data showing efficacy in CNS myeloma, the use of IMIDs in this setting requires further examination. The use of agents like thalidomide and lenalidomide as induction treatment have achieved high rates of partial and complete remission[15] and appear to penetrate the blood brain barrier.[16]

HSCT has shown a clear benefit and significant progression-free survival in multiple myeloma patients.[14,15] The use of autologous and allogenic stem cell transplantation in CNS myeloma case reports reported disease remission of up to 12 months.[17]

CNS MM is an aggressive condition and, even with modern therapies, remains highly lethal with a median overall survival of only 4-6

months.[2] Small number of patients can achieve longer survival with combined treatment such as the case presented here.

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