Leukemia Research Reports 14 (2020) 100210

Contents lists available at ScienceDirect

Leukemia Research Reports

journal homepage: www.elsevier.com/locate/lrr

Letter to the Editor

# Management of central nervous system involvement in multiple myeloma after autologous hematopoietic stem cell transplantation

ABSTRACT

Multiple myeloma (MM) is characterized by uncontrolled clonal proliferation of plasma cells, mainly in bone marrow, and its extramedullary involvement is rare. Central nervous system involvement in MM is a highly aggressive disease with a survival of less than 6 months. The best treatment regimen for MM with CNS involvement is still unknown and in most patients, the prognosis is unfavorable. To date, there is no report of CNS involvement without evidence of systemic involvement in a known case with MM. Here, we report a 58-year-old male with MM who recurred CNS involvement without evidence of systemic involvement following autologous stem cell transplant.

## Letter to the editor

Multiple myeloma (MM) is characterized by uncontrolled clonal proliferation of plasma cells, mainly in bone marrow, and its extramedullary involvement is rare. The incidence of extramedullary plasmacytomas is 7% to 18% at MM diagnosis and up to 20% at relapse [1]. The presence of extramedullary involvement in MM represents aggressive disease, and is associated with shorter overall and progression-free survival [2]. Extramedullary involvement occure in commonly the nasopharyngeal, larynx, skin, upper respiratory tract, and central nervous system (CNS) [3]. The CNS involvement of the MM, is defined by the presence of plasma cells in the cerebrospinal fluid (CSF) in a patient with MM. It is considered extremely rare and estimated only in 1% of patients. The best treatment regimen for MM with CNS involvement is still unknown and in most patients, the prognosis is unfavorable [4]. To the best of our knowledge, this is the first published report of CNS involvement without evidence of systemic involvement in a known patient with MM relapse following autologous stem cell transplant.

In October 2015, a 58-year-old male was presented to Hematology, Oncology and Stem Cell Transplantation Research Center; Tehran University of Medical Sciences, Tehran, Iran, with complaints of bone pain and decreased urine volume about 2 months prior to admission. Initial laboratory findings demonstrated a normocytic, normochromic anemia with a hemoglobin of 8.2 g/dL (normal, 14–18 g/dL), a white blood cell count (WBC) of 6500 cell/mm$^3$ (normal, 4–11 × 10$^9$/L), and a platelets count of 245,000 × 10$^9$/L (normal, 150–450 × 10$^9$/L). He had a creatinine of 4.2 mg/dL (normal, 0.6–1.3 mg/dL), calcium of 12.5 mg/dL (normal, 8.5–10.5 mg/dL), albumin of 3.7 g/dL (normal, 3.4–5.4 g/dL), total protein of 11.7 g/dL (normal, 6–8.3 g/dL), lactate dehydrogenase (LDH) of 970 U/L (normal, 100–190 U/L), beta-2 microglobulin of 13.8 mg/L (normal, 0–3 μg/mL), and an erythrocyte sedimentation rate (ESR) of 135 mm/hr (normal, 0–20 mm/hr).

Serum protein electrophoresis (SPEP) and immunofixation electrophoresis (IFE) were performed that demonstrated immunoglobulin G kappa monoclonal gammopathy in the gamma-globulin region. A bone marrow biopsy showed more than 80 percent involvement by abnormal appearing plasma cells, confirmed by CD138+ immunohistochemical stain (Fig. 1). In addition, a thorough cytogenetic evaluation revealed the deletion of 1q21 and t(4;14). A skeletal survey showed multiple well-defined lytic lesions (punched-out lesions) in the skull. Based on the Revised International Staging System (R-ISS), the diagnosis of stage III multiple myeloma was established.

The patient completed induction therapy with bortezomib-cyclophosphamide-dexamethasone (VCD) regimen and achieved a complete response after 4 courses of treatment. After the treatment period, the general condition of the patient was stabilized, the renal function was completely improved and all laboratory parameters were within the normal range. A repeat bone marrow biopsy following treatment did not show any evidence of multiple myeloma.

In August 2016, the patient was scheduled for autologous bone marrow transplantation. Single-agent high-dose Melphalan at the dosage of 200 mg/m$^2$ was used as a conditioning regimen prior to an autologous stem cell transplant. Bone marrow transplantation was performed successfully without any complication. Subsequently, the patient was placed on Lenalidomide maintenance (at a dose of 25 mg per day, on days 1 to 21 of each 28-day cycle) one month after the autologous bone marrow transplantation. During his follow-up within 5 months after the transplant, the patient had no clinical problems. After 5 months of transplantation, the patient suffered from severe headache and pelvic pain. At this time, the results of laboratory tests showed a hemoglobin of 13.6 g/L (normal, 13.5–18.0 g/L), a WBC of 8700 cell/mm$^3$ (normal, 4000–11,000 cell/mm$^3$), a platelet count of 245 × 10$^9$/L (normal, 150–450 × 10$^9$/L), serum creatinine, 1.4 mg/dL (normal, 0.6–1.3 mg/dL), calcium of 9.5 mg/dL (normal, 8.5–10.5 mg/dL), LDH of 580 U/L (normal, 100–190 U/L), beta-2 microglobulin of 4.1 mg/L (normal, 0–3 mg/mL), and an ESR of 65 mm/hr (normal, 0–20 mm/hr).

In fundoscopic examinations, bilateral pupil edema was detected. A lumbar puncture was performed and CSF smear revealed the presence of several plasma cells suggestive of CNS involvement (Fig. 2), which indicated a relapse of the MM. Interestingly, results of other diagnostic tests such as serum and urine protein electrophoresis with immunofixation, and serum free light chains were all in the normal range. In addition, bone marrow aspiration and biopsy showed a normocellular bone marrow with no increase in plasma cell count. Flow cytometry was performed on bone marrow aspiration sample, and the results showed no abnormal findings. Fluorescence in situ hybridization (FISH) analysis identified 17p deletion and translocation t(4;14).

The patient was consulted with Dr. James R. Berenson, who is the

https://doi.org/10.1016/j.lrr.2020.100210
Received 15 October 2019; Received in revised form 16 May 2020; Accepted 5 June 2020
Available online 10 June 2020

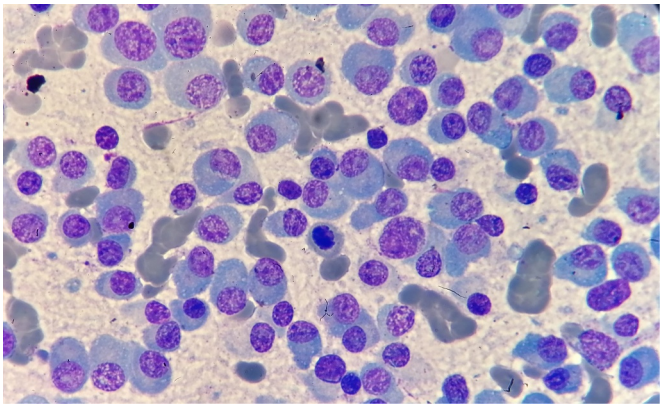

**Fig. 1.** Bone marrow aspiration showing a markedly proliferation of abnormal plasma cells.

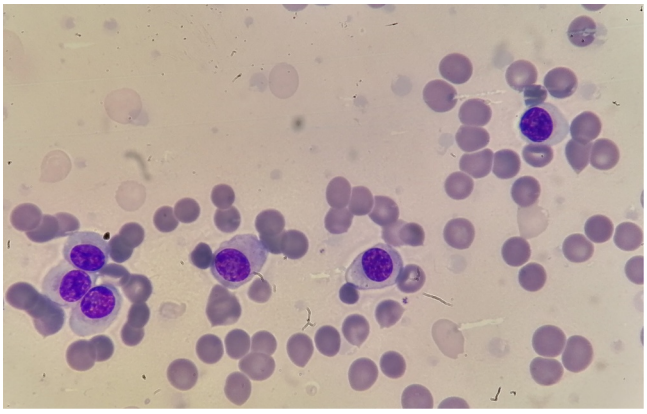

**Fig. 2.** Cerebrospinal Fluid (CSF) smear showing the presence of several plasma cells.

Founder, President and Chief Executive Officer of the Institute for Myeloma and Bone Cancer Research (IMBCR). Dr. Berenson suggested the DKBP-BD treatment regimen to be the best option in our patient. The **DKBP-BD** regimen consisted of a 28-day cycle of **D**examethasone (40 mg as a 30-minute intravenous infusion on days 1, 8, 15, and 22), **K**yprolis® (Carfilzomib) [56 mg/m$^2$ as a 10-minute infusion on days 1, 8, and 15 (a dose of 20 mg per square meter was chosen as the starting dose)], **B**endeka® (bendamustine) [70 mg/m$^2$ as a 10-minute intravenous infusion on days 1 and 2], **P**omalyst® (pomalidomide) [4 mg once daily orally on days 1 to 21 of a 28-day cycle], **B**iaxin® (clarithromycin) [500 mg every 12 h orally on days 1 to 28], **D**arzalex® (daratumumab) [16 mg/kg intravenous once weekly for 8 weeks (weeks 1 to 8); then 16 mg/kg every 2 weeks for 16 weeks (weeks 9 to 24); and then 16 mg/kg every 4 weeks thereafter]. Patient also received antiviral prophylaxis (acyclovir 200 mg orally twice daily), 81 mg of aspirin daily, Alpha-Lipoic Acid supplement 600 mg orally daily for the prevention of neuropathy (don't take it on the day of Kyprolis), Vitamin D and Calcium supplements, Allopurinol 300 mg orally daily, and zoledronic acid (Zometa) 4 mg intravenous once monthly. Given the lack of some agents of this regime in Iran, the patient was referred to Spain for receiving this treatment regimen. After 6 months of treatment with DKBP-BD regimen, the patient was in complete remission.

This case highlights that CNS involvement without evidence of systemic involvement can occur during relapse of MM following autologous stem cell transplant. It can be suspected in the presence of neurological manifestations at any time after the initial diagnosis of MM [5]. CNS involvement in MM is a highly aggressive disease that its survival has been reported to be less than 6 months. It has been reported that long-term survival can be achieved through a combination of multi-dosing Intrathecal chemotherapy, radiation, and Immunomodulation-based therapy [6]. Results of a study revealed that CNS involvement in MM is associated with elevated levels of beta-2-microglobulin, high LDH level, and secondary plasma cell leukemia [7]. Our patient's course suggests that clinicians should be aware of this rare but aggressive complication of MM following autologous stem cell transplant.

## Contribution

K.M.F. collected patient data; and N.M. wrote, reviewed and edited the manuscript.

## Declaration of Competing Interests

We declare that there is no competing financial interests in our article.

## References

[1] J. Bladé, C. Fernández de Larrea, et al., Soft-tissue plasmacytomas in multiple myeloma: incidence, mechanisms of extramedullary spread, and treatment approach, J. Clin. Oncol. 29 (28) (2011) 3805–3812.
[2] M. Varettoni, A. Corso, G. Pica, S. Mangiacavalli, C. Pascutto, M Lazzarino, Incidence, presenting features and outcome of extramedullary disease in multiple myeloma: a longitudinal study on 1003 consecutive patients, Ann. Oncol. 21 (2) (2010) 325–330.
[3] A.L.M.S. Dias, F. Higashi, A.L.M. Peres, P. Cury, E.Q. Crusoé, V.T.M Hungria, Multiple myeloma and central nervous system involvement: experience of a Brazilian center, Rev. Bras. Hematol. Hemoter. 40 (1) (2018) 30–36.
[4] A.B. Fassas, F. Muwalla, T. Berryman, et al., Myeloma of the central nervous system: association with high-risk chromosomal abnormalities, plasmablastic morphology and extramedullary manifestations, Br. J. Haematol. 117 (1) (2002) 103–108.
[5] A. Jurczyszyn, N. Grzasko, A. Gozzetti, J. Czepiel, A. Cerase, V. Hungria, et al., Central nervous system involvement by multiple myeloma: a multi-institutional retrospective study of 172 patients in daily clinical practice, Am. J. Hematol. 91 (6) (2016 Jun) 575–580.
[6] C.I. Chen, E. Masih-Khan, H. Jiang, A. Rabea, C. Cserti-Gazdewich, V.H. Jimenez-Zepeda, et al., Central nervous system involvement with multiple myeloma: long term survival can be achieved with radiation, intrathecal chemotherapy, and immunomodulatory agents, Br. J. Haematol. 162 (4) (2013 Aug) 483–488.
[7] A.O. Abdallah, S. Atrash, Z. Shahid, M. Jameel, M. Grazziutti, S. Apewokin, et al., Patterns of central nervous system involvement in relapsed and refractory multiple myeloma, Clin. Lymphoma Myeloma Leuk. 14 (3) (2014 Jun) 211–214.

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