

Elevated cerebrospinal fluid β -2 microglobulin as a tumor marker in a patient with myeloma of the central nervous system

Enaam M. Alsobhi, MD, MRCPATH, Ibrahim A. Hashim, PhD, DABCC, Mohammad A. Abdelaal, FRCPI, FRCPath, Ahmad M. Aljifri, MB, MSC, Abdelrahman M. Alshamy, MD, DIS.

ABSTRACT

Myeloma involvement of the nervous system is rare. Extensive literature review revealed only a few cases reported from different parts of the world. The presence of CNS symptoms and detection of plasma cells in the CSF is the usual basis of diagnosis. In addition, immunoelectrophoresis and immunofixation for detection of monoclonal protein confirm the diagnosis in some cases, while some authors used flow cytometry and cytogenetic studies on CSF. Reports of multiple myeloma also include unfavorable cytogenetic abnormalities of chromosome 13. We report a case with relapsed CNS multiple myeloma with the detection of elevated β -2 microglobulin (β 2M) as a tumor marker in the CSF.

Saudi Med J 2007; Vol. 28 (1):128-130

From the Departments of Pathology and Laboratory Medicine (Al-Sobhi, Abdelaal, Aljifri) and the Department of Medical Imaging (Alshamy), King Khalid National Guard Hospital, Jeddah, Kingdom of Saudi Arabia, and the Department of Pathology (Hashim), University of Texas Southwestern Medical Center, Dallas, United States of America.

Received 27th February 2006. Accepted 13th June 2006.

Address correspondence and reprint request to: Dr. Enaam M. Alsobhi, Consultant Hematologist, King Khalid National Guard Hospital, PO Box 9515, Jeddah 21423, Kingdom of Saudi Arabia. Tel. +966 (2) 6240000. Fax. +966 (2) 6240000 Ext. 1240. E-mail: ensobhi@hotmail.com

Monoclonal proliferation of an immunoglobulin secreting plasma cell characterizes multiple myeloma (MM).¹ Patients with MM often have neurological complications either due to metabolic disorders such as hypercalcemia, uremia, and hyperviscosity,² or due to peripheral neuropathy, spinal cord

compression, and cranial nerve infiltration.^{3,4} Isolated CNS multiple myeloma (CNS-MM) is rare and can arise from the calvarium, dura, or cranial base.⁵ Intracranial plasmacytoma is more common in females, who represent approximately 89% of patients with CNS-MM in some centers.¹ Leptomeningeal MM is extremely rare.³ The presence of CNS symptoms and detection of plasma cells in the CSF is the usual basis of diagnosis. Other laboratory investigations performed on the CSF include immunoelectrophoresis, immunofixation, flow cytometry, and cytogenetic analysis. Radiology was performed on some patients as part of investigations. However, myeloma can simulate hemangioma in some cases.⁶ The performance of β 2M as tumor marker in CSF for CNS-MM is not well documented. Some reports show raised levels in the CSF of patients with leukemia/lymphoma,⁷ however, few reports show raised levels in the CSF of patients with CNS-MM.⁸ We report a case of MM with CNS involvement with elevated β 2M in the CSF at presentation.

Case Report. The patient is a 60-year-old Saudi diabetic female with good glycemic control. She was diagnosed with MM stage III (Durie-Salmon and international staging system) 14 months earlier. On presentation, she reported generalized bone pain. Investigations showed serum monoclonal paraprotein (typed as immunoglobulin G Kappa) at a concentration of 51 gm/l. Elevated β 2M at 6 mg/l (normal range <1.9 mg/l) No Bence-Jones protein was detected in urine. Hemoglobin was low at 8gm/dl. Skeletal survey showed multiple lytic lesions involving the skull and dorsolumbar regions. A CT scan showed fracture of T9. Bone marrow aspiration results were inconclusive. Serum urea, creatinine, and calcium concentrations were within normal limits. The patient received 6 cycles of chemotherapy using cyclophosphamide, oncovin, and prednisolone (COP) and palliative radiotherapy for the lower back. She underwent complete remission with reduction of serum paraprotein concentration to <9 gm/l and a fall in serum β 2M to normal levels. Hemoglobin was 12.5 g/dl with normal lactate dehydrogenase level. Twelve months following initial presentation she presented to the emergency room with headache, blurring of vision, and pain in the middle of the left thigh. Examination revealed papilledema and tenderness

in the middle of the thigh. Assessment of her MM status showed no serum paraprotein detected, and bone marrow aspiration was normal. Hemoglobin, urea and creatinine, β 2M, and calcium profile were within normal limits. A skeletal survey showed a new lytic lesion in the mid shaft of the femur. A CT scan and MRI of the brain showed an extra axial lesion in the right occipital region of approximately 1.7 cm x 1.1 cm, and a small lesion on the right side of the fourth ventricle, suggestive of multiple myeloma or hemangioma (Figures 1 & 2). The presence of plasma cells in the CSF examination confirmed myeloma involvement of the CNS (Figure 3). The protein level in the CSF was high at 48gm/l. The CSF protein electrophoresis followed by immunofixation showed IgG kappa. The plasma cell was positive for CD56, and negative for CD19. The β 2M level of the CSF was high at 2.8 mg/l (1.3 +/- 0.7 mg/l in healthy subjects), measured using IMX autoanalyzer (Abbott laboratories, Abbot Park, Illinois, U.S.A). The chromosomal analysis in the CSF failed. We managed her with triple intrathecal chemotherapy (Methotrexate, Ara-C and hydrocortisone) and adjuvant cranial radiotherapy. She underwent intramedullary nail fixation to the left femur. Though she showed some response to the above chemotherapy treatment, she deteriorated rapidly and developed quadriplegia. She refused further investigations. Her conscious level started to deteriorate. She received supportive treatment and continuous morphine infusion in the form of PCA to control her pain, and she passed away after a short period.

Discussion. The detection of malignant plasma cells in the CSF in the presence of suggestive symptoms defines involvement of the CNS with MM.³ Involvement may present as diffuse leptomeningeal or less often as a solitary intracranial lesion.^{3,8} In our patient, the involvement was a leptomeningeal and intracranial lesion. We do not know the incidence of CNS involvement with MM, but there is general agreement that it is rare,^{2,9} however, there are 2 reported series of 23 and 18 patients.^{2,3} In these series the most common CNS infiltration was leptomeningeal. The neurological symptoms related to a tumor type lesion in our patient. Previous studies report that the median interval from the MM diagnosis and involvement of CNS is approximately 9-11 months.^{3,9} However, there is documented CNS involvement after 10 years in one of the cases.⁹ In our patient, we diagnosed the CNS involvement one year following the MM diagnosis, which is in agreement with the reported time in the published literature. Similarly to previous studies, we based the diagnosis on high CSF protein and the presence of plasma cells in the CSF;^{2,3} however, there were 2 cases recently published where the CSF had no plasma cells detected.⁹ Other laboratory tests such

as monoclonal band in protein electrophoresis of the CSF, will support the diagnosis, and positive radiological findings were found to be useful as confirmatory tests in the diagnosis of this condition.^{5,6} We detected all these confirmatory tests in our patient. The CD56 is usually negative in normal plasma cells.¹ Studies report positive expression for CD56 in 66% of myeloma related lesions,¹ however, a recent study reported CD56 negativity in

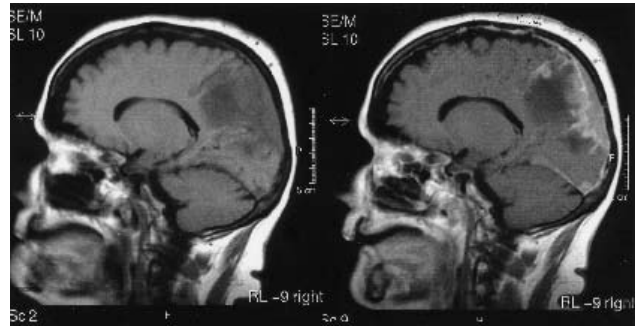


Figure 1 - Magnetic resonance image (T2) showing pre and post contrast equivalent axial plane demonstrate a dural mass invading the superior sagittal sinus, leptomeningeal enhancement and suggestion of adjacent gyral invasion.

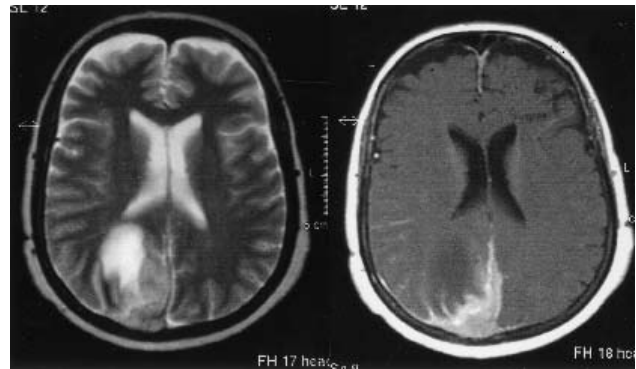


Figure 2 - Magnetic resonance image pre and post contrast injection demonstrating dural mass and diffuse leptomeningeal enhancement.

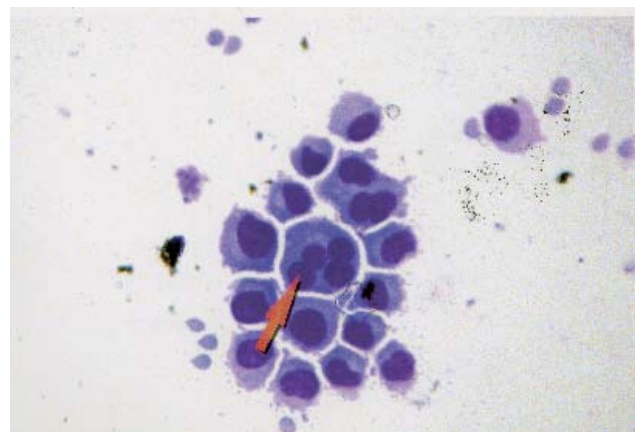


Figure 3 - Plasma cells in the CSF, some are multinucleated (arrow).

3 cases.⁹ In our case, the plasma cells in the CSF were positive for CD56. Reports show MM involving the CNS to have a high frequency of chromosome 17p13.1 (p53) deletions.¹⁰ Studies also report an association with unfavorable cytogenetic abnormalities in myeloma of the CNS, especially translocation or deletion of chromosome 13,³ however, we did not detect this in our patient. Beta 2 microglobulin is a low molecular weight protein integrating the light chain HLA antigens. Its serum concentration increases in different neoplasias and in renal failure.^{8,12} High serum β2M carries a poor prognostic marker in patients with MM.¹² Some of the previous studies did not clearly define the significance of the level of β2M in CSF for patients with MM,^{7,8} particularly as a prognostic factor or as a monitoring test for CNS involvement in MM. We found significant elevation of β2M in the CSF of our case at the time of diagnosis, but this reduced markedly after intrathecal treatment with chemotherapy, and later clearing of plasma cells from the CSF followed by normalization of β2M in the CSF. The discrepancy between CSF and serum β2M levels suggests intrathecal production. The disease has a high mortality, and poor prognostic outcome.³

There are several suggested modalities of treatment for MM with CNS involvement, including intrathecal and systemic chemotherapy, with or without radiotherapy.³ The remission period is usually short if achieved,^{1,3} and survival rate is very low. In our case, we treated her with intrathecal chemotherapy and subsequent radiotherapy. Systemic chemotherapy was planned, but her condition deteriorated rapidly, and she died.

In conclusion, we know that CNS involvement in MM is rare and has a poor prognosis, and we have not yet clearly delineated the usefulness of β2M as a prognostic maker in the CSF and monitoring its level in CSF in patients with CNS involvement. This clearly warrants further study with a large number of patients for this fatal condition.

Acknowledgment. *We would like to acknowledge the help of Professor A. Omar from the Department of Hematology, King Abdul-Aziz and Oncology Hospital in Jeddah, for his assistance in preparing the manuscript, and Miss Wafa Fakhraldin for providing technical and library facilities.*

References

1. Schwartz TH, Rhiew R, Isaacson SR, Orazi A, Bruce JN. Association between intracranial plasmacytoma and multiple myeloma: clinicopathological outcome study. *Neurosurgery* 2001; 49: 1039-1044.
2. Fassas AB, Muwalla F, Berryman T, Benramdane R, Joseph L, Anaissie E, et al. Myeloma of the central nervous system: association with high-risk chromosomal abnormalities, plasmablastic morphology and extramedullary manifestations. *Br J Haematol* 2002; 117: 103-108.
3. Schluterman KO, Fassas AB, Van Hemert RL, Harik SI. Multiple myeloma invasion of the central nervous system. *Arch Neurol* 2004; 61: 1423-1429.
4. Movsas TZ, Balcer LJ, Eggenberger ER, Hess JL, Galetta SL. Sixth nerve palsy as a presenting sign of intracranial plasmacytoma and multiple myeloma. *J Neuroophthalmol* 2000; 20: 242-245.
5. Willinsky RA, Cooper PW, Kassel EE. CT of myeloma involving the skull base. *J Can Assoc Radiol* 1985; 36: 328-331.
6. Kujat C, Reiche W, Koch B, Moringlane JR. Rare intracranial plasmacytoma manifestations. Case reports and review of the literature in diffuse plasmacytoma, in primary solitary extramedullary plasmacytoma in primary solitary osseous plasmacytoma. *Radiologe* 1996; 36: 914-920.
7. Hansen PB, Kjeldsen L, Dalhoff K, Olesen B. Cerebrospinal fluid beta-2-microglobulin in adult patients with acute leukemia or lymphoma: a useful marker in early diagnosis and monitoring of CNS-involvement. *Acta Neurol Scand* 1992; 85: 224-227.
8. Rodriguez MA, Lira P, Eoradori A, Grebe G. Beta 2 microglobulin in some hematologic neoplasms. *Rev Med Chil* 1989; 116: 538-542.
9. Pontikoglou C, Fragos C, Kolyvaki E, Samonis G, Eliopoulos GD, Papadaki HA. Multiple myeloma involving the central nervous system: a report of two cases with unusual manifestations. *Leuk Lymphoma* 2005; 46: 737-741.
10. Chang H, Bartlett ES, Patterson B, Chen CI, Yi OL. The absence of CD56 on malignant plasma cells in the cerebrospinal fluid is the hallmark of multiple myeloma involving central nervous system. *Br J Haematol* 2005; 129: 539-541.
11. Chang H, Sloan S, Li D, Keith Stewart A. Multiple myeloma involving central nervous system: high frequency of chromosome 17p13.1 (p53) deletions. *Br J Haematol* 2004; 127: 280-284.
12. Bettini R, Redaelli S, Maino C, Bertuol S, Costantini C, Lazzarini A, et al. [Prognostic value of serum beta2-microglobulin in multiple myeloma] *Recenti Prog Med* 2005; 96: 81-86.