Review

Multiple myeloma of the central nervous system: a clinicopathological review

E. Al-Sobhi, A.O. Osoba, A. Karar and A.M. Zuraiki

ABSTRACT Multiple myeloma (MM) is a systemic malignancy of pathologic plasma cells that is treatable with chemotherapeutic agents and irradiation, but rarely curable. The spectrum of neurological complications of MM is diverse; however, involvement of MM in the cerebrospinal fluid and leptomeningeal infiltration is considered rare. There have been many reviews of central nervous system complications in MM but there are none on intracranial and leptomeningeal infiltration of MM. We review this here along with our clinicopathological experience and a summary of our present knowledge of this condition.

Atteinte du système nerveux central par le myélome multiple : examen clinicopathologique

RÉSUMÉ Le myélome multiple est un cancer systémique caractérisé par des cellules plasmatiques anormales, qui peut être traité par des agents chimiothérapeutiques et par irradiation, mais qui est rarement curable. Le spectre des complications neurologiques du myélome multiple est large ; toutefois, l’envahissement du liquide céphalorachidien par le myélome multiple et l’infiltration leptoméningée sont considérés comme rares. Il existe de nombreuses études consacrées aux complications du MM au niveau du système nerveux central, mais il n’en existe aucune sur l’infiltration intracrânienne et leptoméningée. Nous présentons ici une analyse de cette question, ainsi que notre expérience clinicopathologique et un résumé de nos connaissances actuelles sur cette maladie.

1Department of Haematology; 2Department of Microbiology; 3Department of Oncology, King Khalid National Guard Hospital, Jeddah, Saudi Arabia (Correspondence to E. Al-Sobhi: ensobhi@hotmail.com).
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Introduction

Multiple myeloma (MM) is a cancer of the plasma cells. Malignant plasma cells in bone marrow produce an immunoglobulin, usually monoclonal IgG or IgA or, less commonly, immunoglobulin light chains [1]. Very rarely IgD [2] or both IgG and IgA, or even no immunoglobulins are produced (non-secretory MM) [1,3]. MM is characterized by monoclonal paraprotein production, lytic lesions and increased plasma cells in the bone marrow [7]. The most common complications include renal insufficiency, hypercalcaemia, anaemia and recurrent infection [3,4]. MM is considered an incurable disease despite various methods of treatment, including autologous bone marrow transplantation [3].

There have been many reviews of the central nervous system (CNS) complications in MM but there are none on intracranial and leptomeningeal infiltration of MM. This review focuses on the infiltrative complications and intracranial plasmacytomas with no further discussion of the other possible CNS complications.

CNS involvement in multiple myeloma

Patients with MM often have neurological complications, either due to metabolic disorders such as hypercalcaemia, uraemia and hyperviscosity or due to peripheral neuropathy, spinal cord compression and cranial nerve infiltration [5]. The most common is cord compression and peripheral neuropathy. POEMS syndrome (a conglomerate of clinical features) is another presentation of CNS infiltration [6]. MM involving the CNS (CNS MM) is rare. Leptomeningeal involvement in MM is the most frequent type reported in the literature. Approximately 70 cases have been reported in the published literature in the last 20 years relevant to this subject [5,7].

The largest series, 23 patients with leptomeningeal MM out of 2000 patients with MM, was reported by Schluterman et al. in their institution over a 13-year period [5]. The prevalence of leptomeningeal involvement in MM cases in their series (1.1%) was much lower than that reported in other haematological malignancies, which can be up to 75% in acute leukaemia. The prevalence of leptomeningeal infiltration in breast cancer is about 2%–5% and as high as 26% in small-cell lung carcinoma [5]. The authors concluded that “the reasons underlying the relative paucity of CNS invasion by MM in comparison with other tumours, whether solid or haematological, remain unknown, but might be the result of the underlying biological characteristics, or lack thereof, of malignant plasma cells”.

They reported that the median survival from the diagnosis of MM to development of leptomeningeal MM was 3 months [5]. If survival were prolonged, the prevalence of leptomeningeal MM might be higher. This is a controversial issue since MM is not a curable disease. There are 2 reported cases of patients with MM in which leptomeningeal MM developed after 7 and 10 years (a 65-year-old male and a 64-year-old female respectively) [8], which suggests that it can occur after a long period. However, it does not confirm that a long survival time might increase the prevalence, and a large series over several years might be needed to confirm this.

Involvement of the CNS by MM is determined by the detection of malignant plasma cells in the cerebrospinal fluid (CSF), with the presence of symptoms suggestive of MM [5,9]. Dispenzieri and Kyle, in a review of the neurological aspects of MM, classified the intracranial plasmacytomas or myelomas into 4 groups: those
extending from the skull pressing inward; those growing from the dura mater or the leptomeninges; those arising from the mucous membranes of a nasopharyngeal plasmacytoma; and intraparenchymal lesions without evidence of extension from any of the other 3 sites \[^{10}\]. They noted that CNS involvement in MM is rare, and that magnetic resonance imaging (MRI) and computerized tomography (CT) are useful in the diagnosis of intracranial involvement. However, in our experience, MRI is more sensitive. They further suggested that the differential diagnosis of patients with neurological complaints, especially peripheral neuropathy, should include monoclonal gammopathy of undetermined significance (MGUS), Waldenstrom macroglobulinaemia, POEMS syndrome, amyloidosis and cryoglobulinaemia.

**Pathogenesis of CNS MM**

The association between the intracranial plasmacytoma and progression to MM has not been clearly elucidated; therefore more studies are required to clarify the pathogenesis of CNS infiltration in MM.

Recent attention has focused on the cell adhesion molecules CD56 and CD31 in the pathogenesis of MM. Schwartz et al. studied 9 intracranial plasmacytomas (3 dural, 1 calvarial and 5 cranial base lesions) and concluded that CD56 and CD31 expression was not predictive of the outcome of MM, but that cranial base location of the plasmacytoma was a strong predictor of the development of MM \[^{11}\]. They also reported that several investigators had examined the presence of CD56 in MM cells, MGUS and normal plasma cells. Whereas 50%–80% of MM and monoclonal plasma cells in MGUS expressed CD56, normal plasma cells were CD56-negative. In contrast, Chang et al. concluded that the absence of CD56 on malignant plasma cells in the CSF was the hallmark of CNS MM and that the prevalence of CD56 down-regulation may play a role in the pathogenesis of CNS MM. In their study of 8 patients with CNS MM, 3 had CD56-positive bone marrow myeloma cells and 2 had CSF myeloma cells negative for CD56, while in a control cohort of 84 MM patients without CNS involvement, the bone marrow myeloma cells were CD56-positive in 68 (80%) cases \[^{12}\]. However, in both the above studies the number of patients was too small to allow definitive conclusions.

**Clinical presentation**

CNS involvement by MM can be primary MM or relapsed MM with CNS infiltration \[^{5, 13}\]. Both presentations are considered rare. On presentation, the patients may be known cases of MM presenting with CNS symptoms or new cases in which CNS symptomatology is the clinical presentation of the disease \[^{5, 9}\]. However, other cases may be diagnosed at presentation as solitary intracranial or dural plasmacytoma \[^{14–16}\]. The clinical presentations are based on the degree and the site of infiltration. The symptoms may vary from headache and memory loss to behavioural changes and convulsions \[^{5, 9}\]. However, 2 cases have been reported with unusual manifestations: 1 with the symptoms of diabetes insipidus and hypopituitarism and 1 with obstructive hydrocephalus \[^{8, 17}\]. The duration of developing CNS infiltration has been reported to range from a few months to 2 years after the diagnosis. This indicates that development of CNS infiltration cannot be excluded if the patient does not show CNS symptoms within 2 years. It is not yet known whether
this is related to the pathogenesis of MM progression.

In Schluterman et al.’s series, 21 patients had Salmon-Durie stage III disease and 2 had stage II disease at diagnosis. The median interval from the diagnosis of MM to development of CNS involvement was 13 months [5]. All 23 patients presented with symptoms suggestive of CNS involvement that prompted neurological investigations: 15 patients had cerebral symptoms, including headache, mental status changes and seizures, 12 had cranial neuropathy, while 18 patients had motor and sensory disturbances due to spinal nerve root involvement. Their diagnosis was based on CSF examination, radiology and tissue biopsy. The authors concluded that there were “no distinct neurological symptoms or signs that were specific to the clinical diagnosis of leptomeningeal MM”. However, we noticed from their study that the majority of the cases developed CNS infiltration at a late stage of the disease [5]. It is uncertain if the monoclonal type has a specific association with CNS MM.

Merelli et al. reported 3 cases with peripheral neuropathy in IgD MM [18]. While IgD MM is considered the less frequent type of MM (none of Schluterman et al.’s cases had IgM or IgD MM [5]), we have noticed in our practice that IgD MM patients have more CNS associations compared with other types of MM.

Movsas et al. reported a case with sixth-nerve palsy as a presenting sign for intracranial plasmacytoma in MM [19]. Kyle et al. noted that involvement of cranial nerves and their divisions is a rare complication of MM, which occurs most commonly at the time of progressive disease [20]. The cranial nerves are usually locally distorted or compressed. Sixth-nerve and eighth-nerve palsies may be caused by plasmacytoma involving the petrous bones and the sella [20]. Another rare type of presentation was a 42-year-old woman with Bence–Jones-type MM who developed ocular abnormalities as described by Tuncbilek et al. [21]. Haegelen et al. reported a 72-year-old woman who presented with headaches and left hemiparesis and was diagnosed with dural plasmacytoma; further investigations showed she had systemic MM [22].

Pizzuti et al. reported 3 cases and made a retrospective review of 18 cases with MM infiltration [23]. They found that meningeal involvement occurred in patients with initially stage III MM in 85% of cases and was associated with the occurrence of plasma cell leukaemia in 20% of cases. The most frequent neurological signs were confusion (60%), altered consciousness (25%), gait disorder (25%) and cranial nerve palsy (25%). Diagnosis was based on detection of plasma cells in the CSF.

Diagnosis of CNS MM

The presence of CNS symptoms in MM will usually lead to further investigations, including CSF examination and radiological testing for restaging if the patient was known to have MM.

Laboratory investigations

All routine haematological and biochemical investigations should be performed on MM patients with CNS presentation as a part of disease staging and to exclude primary solitary CNS plasmacytoma. Patients might have hyperproteininaemia, hypercalcaemia [1], evidence of renal failure [9] or increased beta-2-microglobulin (B2M) levels, which is considered to be a poor prognostic factor [24]. Lactate dehydrogenase is usually high [5,8]. Immunoelectrophoresis can be performed on serum as well as CSF in cases where CNS infiltration is suspected, to detect
the monoclonal band and classify the type of immunoglobulin. Fassas et al. reported 18 cases of MM with CNS infiltration, of which 8 had IgG type MM, 5 had IgA, 3 had light-chain disease, 1 had biclonal (IgG and IgA) and 1 had non-secretory MM [9]. Out of 23 patients with CNS MM, Schluterman et al. had 11 patients with IgG type MM, 7 with IgA type, 3 with light-chain disease, 1 with non-secretory disease and 1 with biclonal IgG and IgA MM [5].

CSF examination
Detection of malignant plasma cells in the CSF is considered the hallmark of the diagnosis [13]. Kitamura et al. reported a 52-year-old woman with rare IgD MM and CNS infiltration where the CSF showed 93% of bone marrow cells were malignant plasma cells [16]. In one of our MM patients with CNS involvement, the plasma cells in CSF were multinucleated. The presence of such abnormal morphology indicates malignant infiltration and might suggest an aggressive progress of the disease. This has also been observed by Schluterman et al. [5] and Sham et al. [25]. However, in 2 cases with leptomeningeal MM reported by Pontikoglou et al., no plasma cells were detected in the CSF [8]. Evidence from the literature therefore suggests that plasma cells may be absent in some cases of MM of the CNS. On the other hand, Schluterman et al. noted that frequent CSF examinations might be necessary to confirm the presence of plasma cells, as 2 of their cases were diagnosed only on repeated CSF examination [5]. This may lead to a slight delay in the diagnosis and management of the patient, besides the discomfort from repeated spinal lumbar puncture. We feel that performing protein electrophoresis of the CSF in the absence of plasma cells to confirm the diagnosis is helpful and could aid early diagnosis, especially when this reveals a monoclonal band, as reported in 2 cases by Pontikoglou et al. when plasma cells were negative in the CSF examination [9].

In Merelli et al.’s report of 3 cases with IgD MM they detected and identified IgD paraprotein in the CSF and concluded that there was a “correlation between the presence of the paraprotein in the CSF and the possible neurological involvement” [18]. In our experience in one of our IgG MM cases, the CSF protein electrophoresis and immunofixation confirmed the presence of monoclonal protein IgG.

Tissue biopsy
In some cases, plasmacytoma can be diagnosed by histopathological techniques. Haegelen et al. reported a case diagnosed as IgG-kappa type MM based on microscopic examination and immunohistochemical analysis of the dural plasmacytoma [22].

Radiological investigations
Radiological procedures helpful in the diagnosis of MM of the CNS are CT and MRI. In Tuncbilek et al.’s case of a woman with Bence-Jones-type MM, the authors described the sensitivity of MRI in the findings of ocular and dural myelomatous involvement [21]. However, cerebral or cerebellar manifestations cannot be differentiated from brain tumours by means of CT or MRI [26]. Dural manifestations of plasmacytoma have the same features as meningiomas in CT or MRI [14,25,27]. Mitsos et al. reported a case of plasmacytoma, demonstrated by CT as subdural haematoma [15]. The diagnosis was delayed as the mass was removed and then on the second surgical attempt was diagnosed by sending the tissue for histology. This indicates that plasmacytoma should be considered in the differential diagnosis of patients with MM.
Further investigations

Immunophenotyping
Immunophenotyping of the plasma cells in the CSF and bone marrow using flow cytometry is not a standard procedure if CNS involvement is suspected. However, it will reinforce the diagnosis and can be useful in research cases. Li et al. showed that almost all bone marrow myeloma cells expressed bright CD38 molecules, dim or negative CD45 and negative CD19, whereas the phenotypes for normal plasma cells were CD56-negative and CD19-positive [28]. They concluded that “surface marker analysis of myeloma cells is a useful tool for diagnosis and for further evaluating the prognosis of MM”. However, we think this limited data cannot be the basis for the evaluation of prognosis.

Lin et al. detected that the “combination of CD38 and CD138 was superior to CD38 alone for identifying CD45+ myeloma and separating CD20+ myeloma from B-cell lymphoma”, but nothing was reported in their study regarding CSF [29].

Chang et al. detected CD56-negative plasma cells in the CSF of 2 patients with MM CNS, out of 3 who had positive CD56 in the marrow plasma cells [12]. They concluded that the CD56 negativity on plasma cells in CSF is a hallmark of CNS MM. However this needs further study with a large number of patients to confirm this observation. Kara et al. concluded in their study that cells expressing CD38 and CD45 are involved in the generation of new malignant bone marrow plasma cells and that CD138 expression may be useful in detecting residual disease after autologous stem cell transplantation in MM patients [30]. However, this cannot be the case for CNS myeloma or plasma cells in the CSF as there are no studies to support this view.

Cytogenetic studies
The molecular basis of CNS MM is poorly understood. Chang et al.’s immunofluorescence study of 9 patients suggested that MM is “characterized by translocations involving the immunoglobulin heavy chain (IgH) locus and frequent 13q deletions” and that “alterations of the p53 or c-myc genes in MM may represent secondary changes associated with disease progression” [27]. Fassas et al. reported 18 cases of CNS MM in which the most frequent chromosomal abnormality was translocation and deletion of chromosome 13 [7]. Liebisch and Dohner’s review concludes that MM was characterized by “frequent and complex genomic abnormalities that not only essentially contribute to the pathogenesis of this disease but also reflect its prognostic heterogeneity” [31]. They also reported that while some chromosomal aberrations, such as deletion of chromosome arm 13q, were prognostic markers, the prognostic significance of most other genetic aberrations in MM was undetermined.

In this study there was no suggestion that chromosome 13 abnormalities have an association with CNS involvement in particular. Lee et al.’s study of one case suggested that chromosome 9 may be associated with the pathogenesis of dural extramedullary plasmacytoma [32], but this finding needs more data to support it.

CSF beta 2 microglobulin assay
High levels of B2M in the CSF might help in confirming the diagnosis of CNS infiltration. B2M assay for CSF is not usually recommended routinely in the diagnosis of this condition. However, we have reported recently one case of CNS MM with increased CSF B2M, which we considered a tumour marker and a monitoring test for treatment response [33]. It has been reported by Rodriguez et al. that B2M can be increased in the CSF of the patient with
haematological malignancy with CNS involvement including MM, with no further comment on the significance of the level of B2M in CSF for patients with MM [34].

**Treatment of CNS MM**

MM remains an incurable disease. The 23 cases reported by Schluterman et al. had a median survival from the time of diagnosis of 3 months (ranging from 1 week to 25 months) [5]. All were having intrathecal chemotherapy twice a week with 12 mg methotrexate, 30 mg cytosine arabinoside plus 50 mg hydrocortisone. Cytologic sterilization of CSF was achieved in 11 patients. Systemic chemotherapy was given to 18 patients and the 5 patients who did not receive systemic chemotherapy either died soon after the diagnosis or refused to have further treatment. The authors were of the opinion that the short survival was probably due to aggressive systemic disease and high risk cytogenetic abnormalities of chromosome 13 and multiple chromosomal abnormality in the bone marrow and CSF. Patriarca et al. reported 4 cases with leptomeningeal MM and cerebral MM and in these cases different treatments (including intrathecal chemotherapy, cranial irradiation and systemic chemotherapy), achieved improvement of neurological symptoms in 3 of 4 patients [35]. In these studies the prognosis of the patients was poor, despite aggressive local and systemic treatment even when the CSF was cleared of plasma cells. We have had a similar experience in one of our patients who failed to respond to systemic chemotherapy, intrathecal chemotherapy and radiotherapy. She progressed and developed more extramedullary infiltration and died a few months after the CNS presentation.

Bortezomib, a selective proteasome inhibitor, is a promising new salvage agent for relapsed/refractory MM. Richardson et al. found it to be superior to high-dose dexamethasone in relapsed MM [36]. However, in Gupta et al.’s study of 6 patients treated with bortezomib, 4 developed peripheral neuropathy and 2 developed life-threatening grade 4 motor neuropathy [37]. The cause of the nerve damage remained unclear and its development was unpredictable. While the severity of neurotoxicity and the motor neuropathy seen in their cases is rare (Richardson et al. reported 1% grade IV toxicity), caution is advised especially when using this agent in patients who have received prior neurotoxic therapy or have pre-existing neuropathy [36].

**Conclusion**

In conclusion, most patients with MM progressing to CNS infiltration are those in stage III. We recommend a proper history, detailed clinical examination, with all required investigations for MM diagnosis and staging of the disease. Follow-up will help in making an early diagnosis of leptomeningeal MM. Although CNS MM has a low prevalence, it could be more frequent than expected in high-risk groups, and the investigations should include not only CSF examination but also protein electrophoresis of the CSF in the presence of CNS symptoms. IgD could be associated with CNS infiltration more than other types of MM. CSF examination with positive plasma cells, especially with abnormal morphology remains the hallmark of the diagnosis of CNS infiltration. However, negative CSF examination does not exclude the diagnosis. Protein electrophoresis and repeated CSF examination might be necessary to confirm the diagnosis in some cases.

Chromosome 13 abnormalities indicate poor prognosis in CNS MM, but whether
it is responsible for the progression of MM to CNS involvement is not yet known. We recommend that cytogenetic analysis be performed on all MM patients and consideration of CNS involvement in those with high-risk chromosome 13 abnormalities. Flow cytometry is not usually recommended to confirm the diagnosis. CSF B2M might be of help to monitor the response of intrathecal chemotherapeutic treatment. CSF examination is not recommended as a routine investigation, especially as CNS infiltration in MM is considered rare. However, high CSF B2M levels might help to diagnose early those patients who are susceptible to progression to CNS infiltration although further studies are still required to support this. CNS MM has a poor prognosis and short survival time regardless of the treatment as the patient may die while on treatment or relapse shortly after response to treatment.

References

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Towards a strategy for cancer control in the Eastern Mediterranean Region (WHO-EM/NCD/060/E)

Although the incidence of cancer in the WHO Eastern Mediterranean Region is still well below that in developed countries, the Region is expected to experience the highest increase among all WHO regions in the coming two decades. Prevention therefore offers the greatest public health potential and the most cost-effective long-term approach for cancer control. Towards a strategy for cancer control in the Eastern Mediterranean Region was developed in response to the increasing burden of cancer and the need for coordinated action in this regard.

This publication reflects a shared commitment to reducing the incidence of cancer and improving the quality of life of those who develop cancer. By promoting an integrated approach to the provision of cancer control activities and services, it is hoped the publication will encourage and assist government and nongovernment service providers to work more closely together. The document is available at: http://www.emro.who.int/dsaf/dsa1002.pdf