Extramedullary relapse of myeloma with extensive Central Nervous System involvement

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Case Report

Abstract

Myeloma with Central Nervous System (CNS) involvement is a rare condition. It usually has a very aggressive course and poor prognosis. Here we presented a case of a patient with a history of myeloma who was heavily treated in the past now presented with headache, diplopia and numbness of the chin, Magnetic Resonance Imaging (MRI) scan showed soft tissue mass in the cavernous sinus and diffuse leptomeningeal enhancement in keeping with myeloma relapse with CNS involvement. This case illustrates the extensiveness of extramedullary myeloma relapse in the era of novel agents. Clinicians should be aware of patients with history of myeloma presented with abnormal neurological signs and accordingly, appropriate investigations including MRI imaging should be carried out in order to make the diagnosis.

Keywords: CNS myeloma, Relapse, Extramedullary

Introduction

CNS myeloma is a rare condition, it accounts for about 1% of the disease. With the introduction of new myeloma agents such as proteasome inhibitors, Immunomodulatory Drugs (IMiDs), etc. for the treatment of myeloma relapse, the overall survival of myeloma is increased, but there is also an increased in the incidence of extramedullary relapse. CNS involvement of myeloma is an aggressive extramedullary manifestation of myeloma and usually confers poor prognosis. We reported a case of a patient who was extensively treated in the past for myeloma and relapsed with extensive CNS involvement.

Case presentation

A 65-year-old male was diagnosed with Immunoglobulin A (IgA) myeloma in March 2012. Initial investigations showed 40% of plasma cell infiltration and cytogenetics was normal. He received 6 cycles of CRD (cyclophosphamide, lenalidomide and dexamethasone) as induction chemotherapy and achieved a very good partial response. He then underwent autologous stem cell transplantation and achieved a complete remission. Following that he went on to receive maintenance chemotherapy with lenalidomide and vorinostat.

Fourteen months later his disease relapsed and therefore maintenance chemotherapy was stopped. He was started on bortezomib and dexamethasone as salvage therapy. He completed a total of 7 cycles of bortezomib and dexamethasone and achieved paraprotein immunofixation negativity before treatment was stopped due to neuropathy. Patient remained well afterwards. Seven months later the patient was admitted to the hospital with headache, diplopia, worsening back pain and a lump on the back of the scalp. Examination showed a 6 cm diameter soft tissue mass at the back of the scalp. In addition there was a right sixth nerve palsy and reduced sensation of the chin. No other CNS signs were elicited. Lower limbs showed no obvious motor deficit and no sensory level detected. MRI scan of the head and spine showed diffuse marrow involvement of basal skull including clivus, sphenoid, cavernous sinus and all the calvarium. Both cavernous sinuses also showed infiltration of soft tissues mass (Figure 1).

In addition, there was a large solitary left posterior parietal soft tissue mass arising from the skull vault (figure 2 white arrow). Of note, there was a diffuse meningeal enhancement on T1-weighing after gadolinium enhancement (Figure 2 open arrows) in keeping with extensive leptomeningeal disease involvement.
Discussion

Central nervous system (CNS) involvement of myeloma is very rare, accounting for about 1% of myeloma in current literature. In the context of extramedullary myeloma relapse, however, CNS involvement accounts for up to 21% in one study. In addition, recent studies suggest that there is an increase frequency of CNS myeloma relapse in the era of novel antimyeloma agents. In one small retrospective study, all CNS myeloma relapse patients had received previous autologous stem cell transplant and exposure to at least one previous novel agent (thalidomide, lenalidomide or bortezomib). Whether this is due to improved overall survival with these novel agents is not clear and further studies will be needed to confirm this.

The median time from initial myeloma diagnosis to CNS myeloma relapse is reported to be about 2-3 years from various literatures. Clinical features include cranial and peripheral nerve palsies, headache, cognitive impairment and spinal cord involvement. CNS myeloma predominantly involves dura and leptomeninges. Parenchymal brain disease is very rare. Leptomeningeal disease is best demonstrated by MRI scan with gadolinium enhancement. The frequency of positive MRI evidence of CNS myeloma is variable, in one retrospective analysis, local or diffuse leptomeningeal disease were found in about 59% of patients. In patients with negative MRI findings but high suspicion of CNS myeloma, Cerebrospinal fluid examination will be needed which may show clonal plasma cells.

As CNS myeloma is usually associated with systemic myeloma relapse, restaging investigations of myeloma including serum and urine electrophoresis, free light chain assay as well as bone marrow biopsy (including cytogenetics analysis) are indicated.

Various studies have shown that, like other extramedullary myeloma relapse, CNS myeloma relapse patients usually have other features in keeping with aggressive myeloma (high beta 2 microglobulin, plasmablastic morphology), but most importantly, adverse cytogenetics such as p53 deletion, 13q deletion and translocation involving Immunoglobulin Heavy chain gene, which in turn confer poor prognosis of the condition. In our case, this patient developed new cytogenetic abnormalities with p53 deletion and amplification 1p, which were not seen at initial diagnosis, suggestive of clonal evolution of the myeloma cells following previous treatments.

Evidence based treatment of CNS myeloma is scarce and predominantly come from case reports. Treatment options involved intrathecal chemotherapy, cranial (with or without spinal) radiotherapy. This is usually given in combination with systemic chemotherapy. High dose methotrexate or Cytarabine have been used but with variable outcomes. Furthermore, so far there is no

Figure 1: MRI brain showing infiltration of cavernous sinuses (white arrows) by neoplastic tissues.

Figure 2: Sagittal section of MRI brain (T1 weighted) showing left posterior parietal mass (white arrow) and diffuse meningeal enhancement with gadolinium (open arrows)

Serum electrophoresis showed reappearance of IgA lambda light chain. Bone marrow biopsy showed 80% of plasma cell infiltration with new cytogenetics evidence of p53 deletion and amplification of 1q21. A diagnosis of relapsed myeloma with extramedullary and CNS relapse was made. After discussion with patient and family it was decided to be managed palliative and patient subsequently died 2 months later.
good evidence to support the use of novel antimyeloma agents (bortezomib, thalidomide and lenalidomide) in treating CNS disease. This is largely due to lack of evidence of good penetration through the blood-brain-barrier of these agents as well as lack of clinical data. Whether newer proteasome inhibitors or immunomodulatory drugs show more promising effects awaits further studies.

The outcome of CNS myeloma is poor. Although occasional long term survivors (up to 17 months) have been reported in patients receiving combination of intrathecal chemotherapy, radiotherapy and systemic chemotherapy, data from various other studies shows a median of survival of 7-8 months. Further studies will be needed to address on the treatment of this rare but yet aggressive condition.

Conclusion

CNS myeloma is a rare but an aggressive presentation of extramedullary myeloma relapse. Clinicians should be aware of any neurological presentations of patients with a history of myeloma, especially those who have previous extensive treatments, including novel agents. Prompt investigations for evidence of CNS disease including appropriate imaging such as MRI should be carried out in order to allow early detection and management of the disease.

Conflict of interest

The authors declare that they have no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References