CASE REPORT

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Multiple myeloma invasion of the central nervous system

Zahvatanje centralnog nervnog sistema multiplim mijelomom

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Abstract

Introduction. Multiple myeloma (MM) is characterized by the presence of neoplastic proliferating plasma cells. The tumor is generally restricted to the bone marrow. The most common complications include renal insufficiency, hypercalcemia, anemia and reccurent infections. The spectrum of MM neurological complications is diverse, however, involvement of MM in the cerebrospinal fluid (CSF) and leptomeningeal infiltration are rare considered. In about 1% of the cases, the disease affects the central nervous system (CNS) and presents itself in the form of localized intraparenchymal lesions, solitary cerebral plasmocytoma or CNS myelomatosis (LMM). **Case report**. We presented the clinical course of a 55-year-old man with MM and LMM proven by malignant plasma cells in the CSF, hospitalized with the pain in the thoracic spine. His medical history was uneventful. There had been no evidence of mental or neurological impairment prior to the seizures. Physical examination showed no abnormalities. After a complete staging, the diagnosis of MM type biclonal gammopathia IgG lambda and free lambda light chains in the stage III was confirmed. The treatment started with systemic chemotherapy (with vincristine, doxorubicin plus high-dose dexamethasone – VAD protocol), radiotherapy and bisphosphonate. The patient developed weakness, nausea, febrility, dispnea, bilateral bronchopneumonia, acute renal insufficiency, confusions, headaches and soon thereafter sensomotor aphasias and right hemiparesis. The patient was treated with the adequate therapy including one hemodyalisis. His neurological status was deteriorated, so Multislice Computed Tomography (MSCT) of the head was performed and the findings were normal. Analysis of CSF showed pleocytosis, 26 elements/mL and increased concentrations of proteins. Cytological analysis revealed an increased number of plasma cells (29%). Electrophoretic analysis of proteins disclosed the existance of monoclonal components in the serum, urine and CSF. Immunofixation electrophoretic and quantitative nephelometric tests confirmed Biclonal multiple myeloma of IgG lambda and light chain lambda isotypes. Analysis of neurothropic viruses with ELISA methods was negative. Once the presence of LMM was confirmed, the patient received intrathecal chemotherapy with methotrexate, cytosine arabinoside, dexamethasone three times a week, and systemic high doses of dexamethasone *iv* like a single agent without craniospinale irradiations. Despite the treatment, the patient died one month after the diagnosis. Autopsy was not performed. **Conclusion.** Presented patient, as well as most other patients with MM progressing to CNS infiltration was in the stage III. In addition to the detailed clinical examination, and all investigations required for MM diagnosis and staging of the disease, we introduced the additional CSF examination and calculation of kappa lambda ratio, that helped us make an early diagnosis and prognosis of MM with LMM. Although LMM had a low prevalence, it could be more frequent than expected especially in patients with high risk. CSF examination with positive plasma cells and abnormal morphology remains the hallmark for diagnosing CNS infiltration.

Key words:
multiple myeloma; neoplasm metastasis; brain; diagnosis, differential; immunoglobulins.

Apstrakt

Uvod. Multipli mijelom (MM) karakteriše prisustvo neoplastičnih proliferišućih plazma ćelija, koje se najvećim delom nalaze u kostnoj srži. Najčešća komplikacija oboljenja je pojava renalne insuficijencije, hiperkalcemije, anemije i rekurentnih infekcija. Postoje različite neurološke komplikacije kod bolesnika sa MM, a zahvatanje cerebrospinalnog likvora (CSF) i leptomeninga je retko. Kod oko 1% slučajeva bolest zahvata centralni nervni sistem (CNS) u vidu pojave lokalizovanih intraparenhimskih lezija, solitarnog cerebralnog plazmocitoma ili leptomeningealne mijelomatoze (LMM). **Prikaz bolesnika.** U ovom radu prikazali smo bolesnika, starog 55 godina, sa dokazanim MM i LMM koji je primljen u Kliniku

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za hematologiju VMA zbog bolova u torakalnom delu kičme, bez ranijih značajnijih oboljenja i prethodne neurološke simptomatologije. Nakon učinjenog ispitivanja dokazan je MM tipa biklonalne gamapatije (IgG tipa lambda i slobodnih lakih lanaca tipa lambda) u III kliničkom stadijumu. Nakon primene hemioterapije prema protokolu VAD (vinkristin, doksorubicin plus visoke doze deksametazona), uz radioterapiju i bisfosfonate dolazi do razvoja slabosti, muke, povišene telesne temperature, dispneje, obostrane bronhopneumonije, akutne bubrežne insuficijencije, konfuzije i glavobolje, a brzo posle toga i do senzomotorne afazije i desnostrane hemipareze. Primenjena je adekvatna terapija i jedna hemodijaliza, ali je zbog daljeg pogoršanja neurološkog statusa učinjena multislajsna kompjuterska tomografija (MSCT) glave, čiji je nalaz bio uredan. U daljem toku, zbog sumnje u zahvaćenost CNS osnovnim oboljenjem učinjena je lumbalna punkcija. Analizom likvora viđen je povećan broj ćelijskih elemenata, povećana koncentracija proteina i oko 29% patoloških plazma ćelija. Elektroforezom proteina seruma, urina i likvora potvrđena je monoklonska komponenta, a imunofiksacijom dokazano da se radi o biklonalnoj gamapatiji (IgG tipa lambda i slobodni laki lanaci tipa lambda), uz negativan nalaz neurotropnih virusa, čime je potvrđeno prisustvo LMM. Dalje lečenje sprovođeno je trojnom intratekalnom terapijom uz visoke doze deksametazona, bez primene kraniospinalne iradijacije. Uprkos primenjenom lečenju bolesnik je umro mesec dana nakon dijagnoze MM, a obdukcija nije urađena. **Zaključak.** Većina bolesnika sa MM, kao i prikazani bolesnik, kod kojih je dokazana LMM, nalaze se u III kliničkom stadijumu. Pored detaljne kliničke obrade potrebne za dijagnozu i stepenovanje MM učinili smo ispitivanje likvora i odredili kapa/lambda odnos, što je značajno pomoglo u ranoj dijagnozi LMM. Iako je prevalencija LMM niska, može se češće dokazati kod bolesnika sa MM koji imaju faktore visokog rizika. Ispitivanje likvora sa dokazanim plazma ćelijama koje imaju abnormalnu morfologiju ostaje najznačajniji dijagnostički test za dijagnozu LMM.

Ključne reči:
multipli mijelom; neoplazme, metastaze; mozak; dijagnoza, diferencijalna; imunoglobulini.

Introduction

Multiple myeloma (MM) is characterized by monoclonal paraprotein production, lytic lesions and increased plasma cells in the bone marrow [1]. The most common complications include renal insufficiency, hypercalcaemia, anemia and recurrent infection [2, 3]. Patients often have neurological complications, either due to metabolic disorders such as hypercalcaemia, uremia and hyperviscosity or due to peripherial neuropathy, spinal cord compression and cranial nerve infiltration. The most common are cord compression and peripheral neuropathy [4]. Involvement of the CNS in MM is very rare. Leptomeningeal involvement in MM is the most frequent type of CNS MM reported in the literature. Approximately 70 cases have been reported and published in the literature in the last 20 years [5]. Despite aggressive systemic and local treatment, the outcome was poor [6]. In this study we reported the neurological symptoms and signs, imaging, cerebrospinal fluid (CSF) findings and the clinical course of a 55-year-old man with MM and CNS myelomatosis (LMM). LMM was proven by malignant plasma cells, protein electrophoresis and immunofixation tests of the CSF in the presence of CNS symptoms.

Case report

A 55-year-old man was hospitalized because of thoracic spine pain. His medical history had been uneventful. There had been no evidence of mental or neurological impairment prior to the seizures. Physical examination showed no abnormalities. Initial blood chemistry analyses showed mild anemia (hemoglobine 102 g/L), elevated erythrocyte sedimentation rate of 62 mm/h, fibrinogen 3.59 g/L, increase in serum creatinine, 178 μmol/L, and blood urea nitrogen (BUN) 10.5 mmol/L. The level of β_2-microglobulin was highly increased, 7.99 mg/L, compared to the normal range of 0.7–1.8. Serum albumin and calcium concentrations were normal, but proteinuria was 4.34 g/24 h. Serum protein electrophoresis (PE) on a "Sebia" cappillarys/hydrasys demonstrated a spike in the gamma fraction, as well as in the beta region of urine and CSF PE. Immunofixation electrophoresis (IFE) confirmed that serum M-component belonged to IgG lambda isotype, with concentration of 38.6 g/L on admission, suppressed IgA (< 0.33 g/L) and IgM (< 0.16 g/L), as well as increased value of total lambda free chain (9.2 mg/L). Urinary homogen M-fraction was due to owerflow type of proteinuria and existence of free light chain (FLC) of immunoglobulin (Ig) molecules or Bence Jones proteins. FLC lambda concentration was dramatically elevated to 2490 mg/L as compared to the reference interval of 5.7–26.2 mg/L. Bone marrow aspiration revealed plasma cell infiltration (40%), confirming the diagnosis of multiple myeloma. Magnetic resonance imaging of thoracic spine showed a pathology fracture of Th8 with a decrease in bone intesity near the thoracic spine. Craniogram revealed multiple lytic skull lesions. After a complete staging, we retained the diagnosis of MM type biclonal gammopathia (IgG lambda and free lambda light chains) in the III B clinical stage (CS), and soon, we introduced systemic chemotherapy (VAD protocol) combining vincristine, doxorucin and dexamethasone with bisphosphonate and radiotherapy (single shoot of Th8). Soon thereafter, the patient developed confusions, headaches, weakness, nausea, febrility, dispnea and later sensomotor aphasias and right hemiparesis. After complete examinations (lab analysis, chest rentgenography, echocardiography, microbiology analysis of sputum, bronchoscopy) we concluded that the patient developed bilateral bronchopneumonia and acute renal insufficiency. The patient was treated with adequate antibiotics and other therapy including one hemodyalisis. Because his neurological status deteriorated, we did multislice computed tomography of the head, which was normal. CSF analysis showed pleocytosis (26 elements/mL), increased concentrations of proteins in the CSF, without hypoglicorahia. Cytological analysis revealed an increased number of plasma cells (29%)

(Figure 1). Analysis of neurotropic viruses with ELISA methods was negative twice.

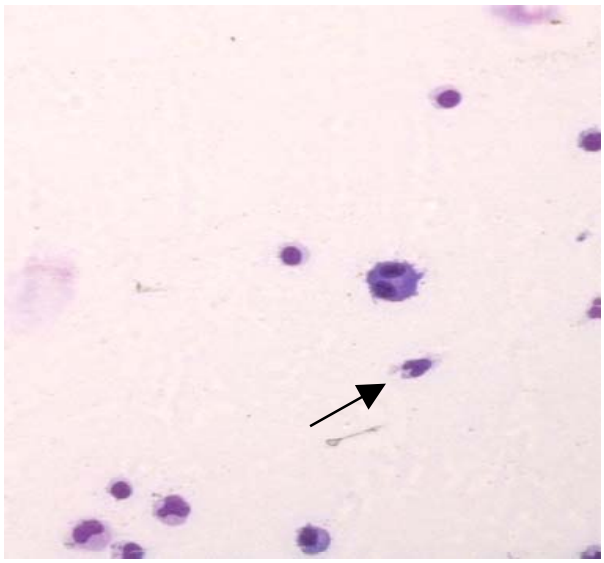

Fig. 1 – High-power view of cytological findings of cerebrospinal fluid (CSF): binuclear plasma cells and mononuclear plasma cells are seen. Other cells are lymphocytes and monocytes

Increased concentration of all three immunoglobulins in CSF and elevated CSF/serum albumin ratio were also detected. Protein imunofixation electrophoresis showed a homogene fraction in CSF for all three immunoglobulines, as mono- or oligoclonal bands (Figure 2), but in serum only for IgG. Besides that, the calculation of kappa/lambda free light chain ratio was decreased (0.006). The concentration of all the mentioned proteins was determined by immunonephelometry ("SIEMENS" DADE BNII) method (Table 1).

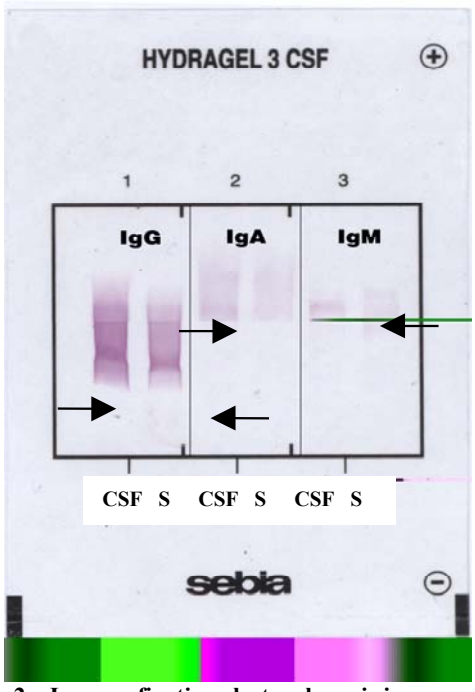

Fig. 2 – Immunofixation electrophoresis in serum (S) and cerebrospinal fluid (CSF)

Table 1
Concentrations of immunoglobulines, Ig fragments and albumin in serum and synovial fluid

Body fluid	Values	(Ref. values)
Cerebrospinal fluid (CSF)		
IgG (mg/L)	330	0–5)
IgM (mg/L)	6.3	0–1
IgA (mg/L)	33	0–5
Albumin	788	0–1
Serum (s)		
IgG (mg/L)	26.7	8–17
albumin (g/L)	35.5	37–53
albumin quotient	22.2	< 5.4
IgG index	0.55	< 0.7
IgG *de novo*		
Free kappa (mg/L)	14.9	
Free lambda (mg/L)	2490	
k/l ratio	0.006	0.26–1.65
CSF/s protein ratio		
IgA index	0.26	0–0.15
IgM index	2.4	0–0.1

After the diagnosis of LMM, the patient received intrathecal chemotherapy with 20 mg methotrexate, 20 mg cytosine arabinoside and 20 mg dexamethasone three times a week, with systemic high doses of dexamethasone *iv* as a single agent without craniospinal irradiations. In spite of the treatment, the patient died one month after being diagnosed. Autopsy was not performed.

Discussion

Patients with MM often have neurologic complications, either due to metabolic disordes such as hypercalcemia, uremia and hyperviscosity or due to peripheral neuropathy, spinal radiculopathies, spinal cord compression and cranial nerve infiltration. While infiltration of leptomeninges by various malignancies including acute lymphocytic leukemia, diffuse lymphomas, breast cancer and small-cell lung cancer with the rates of 2%–75% is well-known, invasion of the CNS in MM is rare, either as presumed localized intraparenchymal lesions, solitary cerebral plasmocytom or as LMM. The overall incidence of CNS involvement was only about 1%. At the time of LMM diagnosis, there was a diffuse array of neurologic symptoms and signs, including cerebral symptoms, neurologic findings referable to cranial neuropathies and to the spinal cord or spinal nerve roots. Presenting symptoms of CNS involvement most commonly include headaches, limb weakness, mental changes and cranial nerve palsies [7–10]. Approximately 70 cases, mostly case reports, have been reported in the English-language literature in the past century. The largest series, 23 patients out of 2,000 patients with LMM was reported by Schluterman et al. [5] from the University of Arcansas Medical Center over a 13-year period. All 23 patients presented with symptoms suggestive of CNS involvement that prompted neurological investigations: 15 patients had cerebral symptoms, including headaches, mental status changes and seizures, 12 had cranial neuropathy, while 18 patients had motor and sensory disturbances due to spinal nerve root involvement. The median

survival from the MM diagnosis to the development of LMM was 3 months. The 23 cases had intrathecal chemotherapy twice a week with methotrexate, cytosine arabinoside plus hydrocortisone. Cytologic sterilization of CSF was achived in 11 patients. Systemic chemotherapy was given to 18 patients and 5 patients who did not receive systemic chemotherapy eather died soon after the diagnosis or refused further treatment. The authors concluded that the reasons underlying a relative paucity of CNS invasion by MM in comparison with other tumors remain unknown, but might be the result of the underlying biological characteristics, or lack thereof, of malignant plasma cells [5].

Pizzuti et al. [11] reported 3 cases and made a retrospective review of 18 cases with MM infiltration. They found that meningeal involvement occurred in patients with initially stage III MM in 85% of cases, and it was associated with the occurrence of plasma cell leukaemia in 20% of cases. The most frequent neuorological signs were confusion (60%), altered consciousness (25%), gait disorder (25%) and cranial nerve (25%) palsy.

If survival was prolonged, the prevalence of LMM might be higher. There are 2 reported cases of patients with MM in which LMM developed after 7 and 10 years suggesting that it can occur after a longer 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 statement [8]. Involvement of the CNS in MM is determined by the detection of malignant plasma cells in CSF, with the presence of symptoms suggestive of MM [5]. Dispenzieri and Kyle [10] in a review of the neurological aspects of MM, classified 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 extencion from any of the other 3 sites.

Movsas et al. [12] reported cases with sixth-nerve palsies as a presenting sign for intracranial plasmacytoma in MM. Kyle and Dispenzieri [9] noted that the involvement of cranial nerves and their divisions is a rare complication of MM, which occurs most commonly at the time of a progressive disease. Other 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 [13]. Haegelen et al. [14] reported a 72-year-old woman presented with headaches and left hemiparesis, and was diagnosed with dural plasmacytoma; further investigations showed systemic MM. Specific magnetic resonance imaging suggestive of CNS invasion included leptomeningeal contrast enhancement and the evidence of meningeal-based lesions sometimes masquerading as intraparenchymal lesions [14]. MSCT of the head in our case raport showed no abnormality.

CSF examination remains the definitive test for diagnosing LMM, usually exhibiting pleocytosis or elevated protein content plus positive cytologic findings [15]. Cytology showed eritrocytes, lymphocytes, and monocytes, but there were also 29% of pleomorphic plasma cells. Pathologic, binucelar plasma cells were also seen.

We systematically measured immunoglobulin levels in sera and CSF samples, and decreased concentration of IgG was expected to the level of 16 g/L after introducing the therapy. Elevated CSF/serum albumin ratio and a significant decrease in filtration capability of blood brain bariere was due to involvement of the CNS in MM. Findings of homogenic fractions in CSF only for IgA and IgM but not in sera, could be connected with their probable local production inside CNS, similar as in cases of Ig intrathecal synthesis [16]. Besides that, extremely low free k/L ratio, as a marker for fast progression and short survival time was also confirmed [17, 18]. These results are in complete concordance with others [19] that imply the quantifications of serum free light chains and calculating FLC k/λ ratio as a useful diagnostic tool for the course and survival.

Merelli et al. [20] reported 3 cases with IgD MM. They detected and identified IgD paraprotein in CSF and concluded that there was a correlation between the presence of paraprotein in CSF and the possible neurological involvement.

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 (diagnosed) with MM. Detection of malignant plasma cells in the CSF is considered the hallmark of the diagnosis. At diagnosis of LMM, intrathecal chemotherapy was given once or twice weekly ranging from 3 to 12 doses, depending on the clinical neurologic response. Systemic treatment consisted of intermediate–dose chemoterapy, high-dose chemoterapy followed by autologous stem cell transplant or followed by allogeneic stem cell transplant. In this case, a standard VAD therapy was introduced with bisphosphonate and radiotherapy (single shoot of Th8). After diagnosis of LMM, we administered three times a week intrathecal chemotherapy with 20 mg methotrexate, 20 mg cytosine arabinoside and 20 mg dexamethasone, with systemic high doses of dexamethasone *iv* like a single agent without craniospinal irradiations.

The prognosis of patients with LMM is poor, despite aggressive local and systemic treatment. The median survival has been estimated at approximately 4–5 months. Even when sterilization of CSF was achieved, patient's survival was limited by the aggressive systemic disease. The most common are high-risk cytogenetic abnormalities in both bone marrow and CSF, plasmablastic morphology, extramedullary manifestations, plasma cell leukemia and high serum lactate dehydrogenase levels. Our previous experience with other Ig isotypes of MM could elicit consideration, that, in this case report, the existence of the second LCD lambda type with CNS involment was more significant for fast progression and worse prognosis. Thus, leptomeningeal seeding is a concomitant of aggressive MM. We believe that the treatment of LMM is indicated, given its potential for symptomatic relief and improvement in the quality of life. Better understanding of the biology of LMM may allow prospective and earlier recognition and treatment of patients at risk for this complication.

Conclusion

Presented patient, as well as most other patients with MM progressing to CNS infiltration was in the stage III. Besides detailed clinical examination, with all the required investigations for MM diagnosis and staging of the disease, we introduced additional CSF examination and calculation of kappa/lambda ratio, that would help us in making an early diagnosis and prognosis of MM with LMM. Although LMM has a low prevalence, it could be more frequent than expected, especially in high-risk patients. CSF examination with positive plasma cells and abnormal morphology remains the hallmark for the diagnosis of CNS infiltration.

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