

MULTIPLI MIJELOM SA DISEMINACIJOM U CENTRALNI NERVNI SISTEM – PRIKAZ SERIJE SLUČAJA

PRIKAZ SLUČAJA

CASE REPORT

MULTIPLE MYELOMA WITH CENTRAL NERVOUS SYSTEM INVOLVEMENT – CASE SERIES

Andrijana Kojić¹, Mila Purić¹

¹ Institut za onkologiju i radiologiju Srbije, Beograd, Srbija

¹ Institute for Oncology and Radiology of Serbia, Belgrade, Serbia

SAŽETAK

Uvod: Multipli mijelom sa diseminacijom u centralni nervni sistem (CNS-MM) predstavlja veoma redak entitet koji čini manje od 1% ekstrapedularnih multiplih mijeloma, a manifestuje se spektrom neuroloških deficita. Modaliteti lečenja mogu biti lokalni, uključujući intratekalnu hemioterapiju i radioterapiju, kao i sistemski, uključujući autolognu/alogeni transplantaciju matičnih ćelija hematopoeze (ATMČH).

Cilj: Prikazujemo iskustvo našeg centra u lečenju ovog retkog entiteta.

Prikaz bolesnika: Kod prve pacijentkinje sa dijagnozom multiplog mijeloma BJ lambda CS IIIA R-ISS 2, verifikovana je tumorska masa u bazi lobanje sa destrukcijom desne sfenoidne i temporalne kosti, koja se manifestovala paralizom *n. facialis-a*. Pacijentkinja je lečena po CVD (ciklofosfamid, bortezomib, deksametazon) protokolu sa postignutom parcijalnom remisijom, tumorska promena je palijativno ozračena, potom je sprovedena autologna transplantacija matičnih ćelija hematopoeze. Lečenje je nastavljeno po DaraRd (daratumumab, lenalidomid, deksametazon) protokolu sa ciljem sprovođenja druge autologne transplantacije matičnih ćelija hematopoeze po produbljivanju remisije. Dosadašnje ukupno preživljavanje iznosi 20 meseci. Kod druge pacijentkinje sa dijagnozom multiplog mijeloma BJ kappa CS IIIA ISS 2, diseminacija u CNS se desila u prvom relapsu bolesti. Sprovedena je zračna terapija endokranijuma, potom je ordinirano sedam ciklusa po PAD (bortezomib, doxorubicin, deksametazon) protokolu sa efektom progresije bolesti i kasnije smrtnim ishodom. Ukupno preživljavanje iznosilo je 48 meseci; preživljavanje od dijagnostikovanja infiltracije CNS-a je bilo 25 meseci.

Zaključak: Uprkos napretku u dijagnostici i lečenju, prognoza za CNS-MM ostaje loša zbog kompleksnog i agresivnog kliničkog ponašanja, a zbog niske incidencije i ograničenosti podataka, postoji potreba za daljim studijama sa ovom malom grupom pacijenata.

Ključne reči: ekstrapedularni multipli mijelom, radioterapija, hemioterapija, transplantacija matičnih ćelija hematopoeze

ABSTRACT

Introduction: Central nervous system involvement in multiple myeloma (CNS-MM) is a very rare entity accounting for less than 1% of all extramedullary multiple myeloma, which manifests as a variety of neurological deficits. Treatment modalities can be locally administered therapy, including intrathecal chemotherapy and radiotherapy, as well as systemic therapy, including autologous/allogeneic hematopoietic stem cell transplantation (AHSCT).

The aim: This article aims to present the experience of our center in the treatment of this rare entity.

Case reports: The first patient was diagnosed with multiple myeloma BJ lambda CS IIIA R-ISS 2 with a tumor mass located at the base of the skull, causing right facial nerve paralysis. The patient underwent six treatment cycles of the CVD (cyclophosphamide, bortezomib, dexamethasone) regimen, achieving partial remission, followed by palliative radiation and autologous stem cell transplantation. The treatment was continued with the DaraRd (daratumumab, lenalidomide, dexamethasone) regimen aimed at a second stem cell transplant which is to be carried out upon deepening remission. The overall survival of the patient, so far, is 20 months. The second patient with multiple myeloma BJ kappa CS IIIA ISS 2 developed CNS involvement with the first recurrence of the disease. Cranial radiation and seven cycles of the PAD (bortezomib, doxorubicin, dexamethasone) regimen were carried out, leading to disease progression and death. The overall survival of the patient was 48 months, with 25 months survival since the diagnosis of CNS infiltration.

Conclusion: Despite advances in diagnosis and treatment, the prognosis for CNS-MM remains poor because of its complex and aggressive clinical behavior. Due to its low incidence, available data are limited indicating the need for further studies involving this small group of patients.

Keywords: extramedullary multiple myeloma, radiotherapy, chemotherapy, hematopoietic stem cell transplantation

Autor za korespondenciju:
Andrijana Kojić
Institut za onkologiju i radiologiju Srbije
Pasterova 14, 11 000 Beograd, Srbija
Elektronska adresa: anakojic95@gmail.com

Corresponding author:
Andrijana Kojić
Institute for Oncology and Radiology of Serbia
14 Pasterova Street, 11000 Belgrade, Serbia
E-mail: anakojic95@gmail.com

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UVOD

Multipli mijelom sa diseminacijom u centralni nervni sistem (CNS-MM) predstavlja veoma redak entitet sa incidencijom manjom od 1% svih ekstramedularnih multiplih mijeloma [1]. U toku protekle decenije primećen je porast incidencije ovog entiteta, prevashodno zbog poboljšanja dijagnostike, lečenja i posledičnog produženja preživljavanja obolelih [2]. Može se dijagnostikovati na početku bolesti, ali se češće utvrđuje u relapsu, odnosno, tokom progresije bolesti [1]. Diseminacija može biti hematogenim putem ili direktnom invazijom, a lezije mogu biti intraparenhimalne i/ili leptomeningealne, sa spektrom neuroloških manifestacija [3]. Pokazano je da je zahvaćenost moždanih ovojnica povezana sa najlošijom prognozom, sa medijanom ukupnog preživljavanja (engl. *median overall survival* – *mOS*) od dva do šest meseci [1,3,4], dok u ostalim slučajevima *mOS* iznosi do 25 meseci [5,6].

Dijagnostička obrada, pored one standardne za multipli mijelom, podrazumeva CT/MR endokranijuma i kičme, lumbalnu punkciju i analizu cerebrospinalne tečnosti, kao i biopsiju tumorskog tkiva [4,7]. Modaliteti lečenja mogu biti lokalni, uključujući intratekalnu hemioterapiju i radioterapiju, te sistemski, uključujući autolognu/alogenu transplantaciju matičnih ćelija hematopoeze (ATMČH) [4].

Uprkos napretku u dijagnostici i lečenju, prognoza za CNS-MM ostaje loša zbog kompleksnog i agresivnog kliničkog ponašanja, nastalog najčešće na terenu progresivne bolesti i usled prethodno sprovedenih terapijskih modaliteta [4,8–10]. Zbog niske incidencije, dostupni podaci su ograničeni, što ukazuje na potrebu za daljim studijama usmerenih na ovu malu grupu pacijenata.

Cilj ovog rada je da prikaže iskustvo našeg centra u lečenju ovog retkog entiteta.

Prikaz slučaja 1

Kod pacijentkinje starosti 62 godine se bolest manifestovala patološkom frakturom leve klavikule i levog humerusa decembra 2022. godine. Na učinjenom CT pregledu opisane su difuzne osteolitičke promene na dugim kostima, vratnim i torakalnim kičmenim pršljenovima i lobanji. Istog meseca je na Institutu za ortopediju Banjica učinjena resekcija i stabilizacija levog humerusa sa biopsijom. Patohistološkim nalazom postavljena je dijagnoza dobro diferentovanog plazmocitoma. Na Institutu za onkologiju i radiologiju Srbije je sprovedena dopunska dijagnostika, marta 2023. godine. U bioptatu koštane srži utvrđena je infiltracija sa 60% patoloških plazmocita. Elektroforezom i imunofiksacijom seruma i urina registrovani su monoklonski lambda laki lanci. Citogenetskom *FISH*

INTRODUCTION

Central nervous system involvement in multiple myeloma (CNS-MM) is a very rare entity with an incidence lower than 1% of all extramedullary multiple myeloma [1]. Over the past decade, an increase in the incidence of this entity was observed, primarily due to the improvement of diagnostics, treatment, and consequent prolongation of survival time of the affected patients [2]. It can be diagnosed at the onset of the disease, but it is more often determined in recurrence, i.e., during the progression of the disease [1]. Dissemination can be hematogenous or by direct invasion, and the lesions can be intraparenchymal and/or leptomeningeal, with an array of neurological manifestations [3]. It has been shown that meningeal involvement is associated with the worst prognosis, with a median overall survival (*mOS*) of two to six months [1,3,4], while in other cases *mOS* is up to 25 months [5,6].

Diagnostics, in addition to the standard procedures for multiple myeloma, include CT/MR of the endocranium and spine, lumbar puncture and analysis of cerebrospinal fluid, as well as tumor tissue biopsy [4,7]. Treatment modalities can be local, including intrathecal chemotherapy and radiotherapy, or systemic, including autologous/allogeneic hematopoietic stem cell transplantation (HSCT) [4].

Despite developments in diagnostics and treatment, the prognosis for CNS-MM remains poor due to its complex and aggressive clinical behavior, stemming most often from the progression of the disease and previously applied therapeutic modalities [4,8–10]. Due to low incidence, available data are limited, indicating the need for further studies aimed at this small group of patients.

This paper aims to present the experience of our center in the treatment of this rare entity.

Case report 1

In the case of a 62-year-old patient, the disease manifested as a pathological fracture of the left clavicle and left humerus, in December 2022. CT imaging revealed diffuse osteolytic lesions in the long bones, cervical and thoracic spinal vertebrae, and the skull. In the same month, resection and stabilization of the left humerus with biopsy were performed at the Institute for Orthopedic Surgery *Banjica*. Pathohistological findings verified the diagnosis of well-differentiated plasmacytoma. Additional diagnostic procedures were carried out at the Institute of Oncology and Radiology of Serbia, in March 2023. Bone marrow biopsy revealed a 60% pathological plasma cell infiltration. Monoclonal lambda light chains were registered with electrophoresis and immunofixation of serum and urine. Cyto-

analizom (engl. *fluorescence in situ hybridization*) detektovane su delecija 13q u 80% nukleusa i delecija TP23 u 25% nukleusa. Postavljena je definitivna dijagnoza multiplog mijeloma *BJ lambda CS IIIA, R-ISS 2*. U daljem toku bolesti došlo je do razvoja periferne paralize desnog *n. facialis-a*, zbog čega je učinjen CT endokranijuma na kome je opisana tumorska promena baze lobanje sa destrukcijom dela desne sfenoidne i temporalne kosti. Otpočeto je lečenje po CVD protokolu (ciklofosamid, bortezomib, deksametazon); ordinirano je šest ciklusa zaključno sa septembrom 2023. godine. Pri reevaluaciji bolesti, u bioptatu koštane srži utvrđeni su: infiltracija sa 25% patoloških plazmocita, vrednosti lambda lakih lanaca u serumu, proteinurija, te vrednost beta2 mikroglobulina u padu za više od 50%. Terapijski efekat procenjen je kao parcijalna remisija. Sprovedena je palijativna radioterapija zaostale promene baze lobanje sa 25 Gy u 10 frakcija, zaključno sa oktobrom 2023. godine. U daljem toku lečenja, pacijentkinja je podvrgnuta autolognoj transplantaciji matičnih ćelija hematopoeze, koja je sprovedena februara 2024. godine. Na proceni terapijskog efekta nakon sprovedene transplantacije, održava se parcijalna remisija. Juna 2024. godine, po ulasku monoklonskog anti-CD38 antitela daratumumaba na pozitivnu listu lekova Republičkog fonda za zdravstveno osiguranje u našoj zemlji, lečenje je nastavljeno po *DaraRd* protokolu (daratumumab, lenalidomid, deksametazon) sa ciljem produbljivanja remisije i sprovođenja druge ATMČH. U toku je drugi ciklus pomenute terapije. Dosadašnje ukupno preživljavanje iznosi 20 meseci.

Prikaz slučaja 2

Kod pacijentkinje starosti 40 godina, bolest se manifestovala naglo nastalom paraparezom, 2012. godine. Učinjen je MR pregled kičme na kome je opisana infiltracija *Th4* pršljenkog tela sa ekstraosealnom paravertebralnom i epiduralnom propagacijom, značajnom stenozom lumena vertebralnog kanala i posledičnom kompresijom kičmene moždine. Tokom jula meseca 2012. godine, na Institutu za ortopediju Banjica, učinjena je dekompresija i stabilizacija segmenta torakalne kičme *Th3-5* uz biopsiju infiltrisanog tela *Th4*. Patohistološki je verifikovan dobro diferentovani plazmocitom. Na Institutu za onkologiju i radiologiju Srbije, sprovedena je kompletna dijagnostička obrada i u bioptatu koštane srži utvrđena je infiltracija patološkim plazmocitima od 80%. Elektroforezom i imunofiksacijom seruma i urina detektovani su monoklonski laki *kappa* lanci. Citogenetska *FISH* analiza nije rađena. Postavljena je dijagnoza multiplog mijeloma *BJ kappa, CS IIIA, ISS 2*. Avgusta i septembra iste

netic *FISH* analysis (fluorescence in situ hybridization) detected 13q deletion in 80% of nuclei and TP23 deletion in 25% of nuclei. A definitive diagnosis of multiple myeloma *BJ lambda CS IIIA, R-ISS 2* was established. In the further course of the disease, peripheral paralysis of the right *n. facialis* developed, which is why a CT scan of the endocranium was performed, revealing a tumorous lesion in the base of the skull with the destruction of a segment of the right sphenoid and temporal bones. The patient was treated with six cycles of the CVD (cyclophosphamide, bortezomib, dexamethasone) regimen, ending in September 2023. Upon reevaluation of the disease, the following were found in the bone marrow biopsy: infiltration with 25% of pathological plasma cells, values of lambda light chains in the serum, proteinuria, and a value of beta2 microglobulin reduced by more than 50%. The therapeutic effect was evaluated as partial remission. Palliative radiotherapy of residual changes in the base of the skull was carried out with 25 Gy in 10 fractions, concluding in October 2023. In the further course of treatment, the patient underwent autologous hematopoietic stem cell transplantation, which was carried out in February 2024. When the therapeutic effect after transplantation was evaluated, the patient was found to be in partial remission. In June 2024, after the monoclonal anti-CD38 antibody daratumumab was added to the positive list of drugs of the Republic Fund of Health Insurance of Serbia, the treatment of this patient was continued with the *DaraRd* (daratumumab, lenalidomide, dexamethasone) regimen, with the aim of deepening remission and conducting a second cycle of AHSCT. The second cycle of this therapy is now in progress. The patient's overall survival to date is 20 months.

Case report 2

In a 40-year-old female patient, the disease manifested as sudden paraparesis, in 2012. An MRI examination of the spine was performed, which revealed infiltration of the *Th4* vertebral body with extraosseous paravertebral and epidural propagation, significant stenosis of the lumen of the vertebral canal, and consequent compression of the spinal cord. In July 2012, at the Institute of Orthopedic Surgery *Banjica*, decompression and stabilization of the *Th3-5* thoracic spine segment were performed, along with a biopsy of the infiltrated *Th4* body. A well-differentiated plasmacyte was verified pathohistologically. A complete diagnostic work-up was carried out at the Institute of Oncology and Radiology of Serbia. Bone marrow biopsy showed an 80% pathological plasma cell infiltration. Monoclonal light *kappa* chains were detected with electrophoresis

godine, sprovedena je palijativna radioterapija zahvaćenog pršljena sa 40 Gy u 20 frakcija. Otpočeta je sistemska terapija po CTD protokolu (ciklofosamid, talidomid, deksametazon); ordinirano je osam ciklusa sa postignutom parcijalnom remisijom (infiltracija koštane srži sa 40% patoloških plazmocita; pad vrednosti κ lanaca za 50%). Usledila je terapija održavanja talidomidom u trajanju od 10 meseci. U junu 2014. godine, dolazi do razvoja neuroloških simptoma u vidu glavobolja, diplopije i nestabilnosti pri hodu. Zbog kliničke sumnje na diseminaciju u CNS učinjena je kompletna dijagnostička obrada; radiografski su opisane difuzne fokalne lezije lobanje uz progresiju nalaza na torakalnim i lumbalnim kičmenim pršljenovima. Na MR pregledu endokranijuma opisana je mekotkivna tumorska promena fronto-parijetalno levo sa infiltracijom moždanog parenhima. U daljem toku je sprovedena zračna terapija endokranijuma u pet frakcija. Lečenje je nastavljeno po PAD protokolu (bortezomib, doxorubicin, deksametazon), ordinirano je sedam ciklusa sa efektom progresije bolesti. Smrtni ishod nastupio je jula 2016. godine. Ukupno preživljavanje iznosilo je 48 meseci, dok je preživljavanje od dijagnoze infiltracije centralnog nervnog sistema do smrtnog ishoda bilo 25 meseci.

DISKUSIJA

Uvidom u dostupnu literaturu ustanovljeno je da u većini studija medijana starosti iznosi preko 60 godina što korelira sa predilekcionom životnom dobu za nastanak multiplog mijeloma u opštoj populaciji [11,12]. Međutim, nekoliko studija je pokazalo da se CNS-MM može javiti i kod mlađih pacijenata [1,5,13,14]. U studiji Čena i saradnika, medijana starosti je iznosila 53 godine [4]. Kod naše pacijentkinje je bolest dijagnostikovana u 40. godini života, što je čini jednom od najmlađih pacijenata sa dijagnostikovanim CNS-MM-om u literaturi. Obolevanje u mlađem životnom dobu može biti povezano sa agresivnijim tokom bolesti. Bolest se dominantno javlja kod ženskog pola [14].

Infiltracija centralnog nervnog sistema se, u većini slučajeva, viđa u relapsu/progresiji bolesti [4,5,7,9,10,13], međutim, u malom broju studija je kod većeg broja pacijenata dijagnostikovana inicijalno [14]. Ono što ovaj entitet čini terapijskim izazovom u slučajevima javljanja u kasnijem toku bolesti jeste refraktornost na prethodno primenjeno lečenje. Agresivnijem kliničkom toku doprinosi i postojanje visoko rizičnih citogenetskih mutacija od kojih su delecija 13q i delecija 17p najčešće [15]. Čang i saradnici su u svojoj studiji dokazali deleciju 17p kod 89% pacijenata [10], dok su Đurčisin i saradnici otkrili deleciju 13q kod 39%, a deleciju 17p kod 23% pacijenata [9]. Kod

and immunofixation of serum and urine. Cytogenetic FISH analysis was not performed. A diagnosis of multiple myeloma BJ kappa, CS IIIA, ISS 2 was established. In August and September of the same year, palliative radiotherapy of the affected vertebra with 40 Gy in 20 fractions was performed. The patient was put on systemic therapy with the CTD regimen (cyclophosphamide, thalidomide, dexamethasone) – she underwent eight cycles achieving partial remission (infiltration of the bone marrow with 40% of pathological plasma cells; decrease in the value of kappa chains by 50%). This was followed by maintenance thalidomide therapy for 10 months. In June 2014, the patient developed neurological symptoms – headaches, diplopia, and unsteady gait. Due to the clinical suspicion of CNS involvement, a complete diagnostic work-up was performed. Radiographically, diffuse focal lesions of the skull were described with progression to the thoracic and lumbar spinal vertebrae. MRI examination of the endocranium revealed a soft tissue tumorous lesion in the left frontoparietal area with infiltration of the brain parenchyma. In the further course, radiation therapy of the endocranium was carried out in five fractions. The patient was treated with seven cycles of the PAD protocol (bortezomib, doxorubicin, dexamethasone), resulting in disease progression. In July 2016, the disease ended in a fatal outcome. The overall survival of the patient was 48 months, while her survival time from diagnosis of central nervous system involvement until death was 25 months.

DISCUSSION

A review of the currently available literature reveals that in most studies the median age of patients is above 60 years, which correlates with the predilection age for the onset of multiple myeloma in the general population [11,12]. However, several studies have shown that CNS-MM can occur in younger patients as well [1,5,13,14]. In a study by Chen et al., the median age was 53 years [4]. Our patient was diagnosed with the disease at the age of 40, which makes her one of the youngest patients diagnosed with CNS-MM documented in literature. The onset of CNS-MM at a younger age may be associated with a more aggressive course of the disease. The disease predominantly occurs in women [14].

Infiltration of the central nervous system is, in most cases, seen in relapse/progression of the disease [4,5,7,9,10,13]. However, a small number of studies show it being diagnosed at the onset in a larger number of patients [14]. What makes this entity a therapeutic challenge in its late stage is its refractoriness to previously applied treatment. The presence of high-risk cytogenetic mutations contributes to a more aggres-

jedne od naših pacijentkinja otkrivena je delecija 13q, dok kod druge pacijentkinje, u vreme dijagnostikovanja, citogenetska analiza nije spadala u dijagnostički standard. Na agresivniji tok bolesti i potencijalnu diseminaciju u CNS može ukazati i povišena vrednost laktat-dehidrogenaze (LDH) koja je jedan od parametara *R-ISS* sistema bodovanja (engl. *Revised International Staging System*) [16]. Naša druga pacijentkinja je imala inicijalno višestruko povišenu vrednost LDH, ali zbog nedostatka *FISH* analize, *R-ISS* skor nije bilo moguće izračunati.

Kliničkom slikom može da dominira spektar neuroloških deficita, kao posledica infiltracije kičmene moždine, kičmenih korenova, moždanih ovojnica ili moždanog parenhima. Kod polovine pacijenata, dominantni simptom je glavobolja praćena vizuelnim smetnjama [14], što je bila manifestacija bolesti jedne od naših pacijentkinja. Neurološka simptomatologija može biti povezana sa metaboličkim stanjem, najčešće hiperkalcemijom, što je često inicijalna manifestacija novodijagnostikovanog multiplog mijeloma [17,18].

Standard lečenja nije jasno definisan i zasniva se na iskustvima sa malim brojem pacijenata. Osim niske incidencije, infiltracija CNS-a često predstavlja kriterijum za isključivanje iz velikih studija koje su usmerene na ispitivanje novih terapijskih modaliteta u lečenju multiplog mijeloma [2,8,14]. Okosnicu sistemskog lečenja čine monoklonska antitela i imunomodulatori koji, za razliku od najčešće korišćenih inhibitora proteazoma, prolaze hematoencefalnu barijeru [19–22]. Radioterapija, kao lokalna terapija, ima najveću primenu u brznoj kontroli neuroloških simptoma [23]. Transplantacija matičnih ćelija hematopoeze predstavlja standard lečenja kod novodijagnostikovanih pacijenata sa multiplim mijelomom koji ispunjavaju kriterijume za transplantaciju, ali u ovoj ograničenoj grupi pacijenata njena efikasnost, način i vreme sprovođenja nisu jasno definisani. Razlog za to jesu kratko vreme preživljavanja, efikasnost kondicionih režima u pogledu penetracije hematoencefalne barijere i očekivane komplikacije same procedure [24,25].

Medijana ukupnog preživljavanja se razlikuje među studijama i u dostupnoj literaturi se kreće od dva do 40 meseci [3,6,9]. Razlike u *mOS*-u su posledica vremena javljanja infiltracije CNS-a, kao i lokalizacije bolesti. U *GIMEMA* studiji je pokazano da su bolje preživljavanje imali pacijenti sa osteoduralnom infiltracijom (*mOS* 25 meseci) naspram pacijenata sa leptomeningealnom infiltracijom (*mOS* 6 meseci) [6]. Kod naših pacijentkinja *mOS* iznosi 34 meseca, dok *mOS* od momenta dijagnostikovanja infiltracije CNS-a iznosi 22,5 meseca, što korelira sa podacima o preživljavanju pacijenata koji

sive clinical course, of which 13q deletion and 17p deletion are the most common [15]. In their study, Chang et al. demonstrated a 17p deletion in 89% of patients [10], while Jurczyszyn et al. found a 13q deletion in 39% and a 17p deletion in 23% of patients [9]. In one of our patients, a 13q deletion was detected, while in the other patient, at the time of diagnosis, the cytogenetic analysis did not fall within the diagnostic standard. An increased value of lactate dehydrogenase (LDH), which is one of the parameters of the *R-ISS* scoring system (*Revised International Staging System*) [16], can also indicate a more aggressive course of the disease and potential CNS involvement. Initially, our second patient had a multiply elevated LDH level, but due to the lack of *FISH* analysis, the *R-ISS* score could not be calculated.

The clinical presentation can be dominated by an array of neurological deficits, resulting from an infiltration of the spinal cord, spinal roots, meninges, or brain parenchyma. In half of the patients, the dominant symptom is headache accompanied by visual disturbance [14], which was the manifestation of the disease in one of our patients. Neurological symptomatology can be related to the metabolic state, most often hypercalcemia, which is often the initial manifestation of newly diagnosed multiple myeloma [17,18].

The standard of treatment is not clearly defined and is based on experience with a small number of patients. Apart from low incidence, CNS involvement is often an exclusion criterion for large studies aimed at investigating new therapeutic modalities in the treatment of multiple myeloma [2,8,14]. The basis of systemic treatment consists of monoclonal antibodies and immunomodulators, which, unlike the most commonly used proteasome inhibitors, can cross the blood-brain barrier [19–22]. Radiotherapy, as a local therapy, is mostly applied in the rapid control of neurological symptoms [23]. Hematopoietic stem cell transplantation represents the standard of treatment in newly diagnosed patients with multiple myeloma who are eligible for transplantation, however, in this limited group of patients, its effectiveness, as well as its method and time of administration, are not clearly defined. The reason for this is the short survival time, the effectiveness of conditioning regimens in terms of penetration of the hematoencephalic barrier, and the expected complications of the procedure itself [24,25].

Median overall survival varies among studies and ranges from two to 40 months in the available literature [3,6,9]. Differences in *mOS* are the result of the time of occurrence of CNS infiltration, as well as the localization of the disease. In the *GIMEMA* study, it was shown that patients with osteodural infiltration (*mOS*

nisu imali leptomeningealnu infiltraciju.

S obzirom na nisku incidenciju javljanja infiltracije CNS-a, ali agresivnu i prirodu brze progresije, potrebno je svaki novonastali neurološki simptom detaljno evaluirati. Poseban diferencijalno dijagnostički izazov predstavlja neurotoksičnost sistemske terapije. Kod naše pacijentkinje kod koje se diseminacija u CNS javila u relapsu bolesti, neurološka manifestacija je diferencijalno dijagnostički mogla odgovarati i neurotoksičnosti primenjene terapije. U literaturi je opisano nekoliko slučajeva razvoja progresivne multifokalne leukoencefalopatije (PML) tokom primene daratumumaba [21]. Najučestalija neurotoksičnost inhibitora proteazoma i imunomodulatora je periferna neuropatija [26,27], posebno tokom kombinovane primene. Trombocitopenije i protrombogene stanja izazvana imunomodulatorima mogu, u retkim slučajevima, biti neposredno povezane sa simptomatologijom moždanog udara [28].

ZAKLJUČAK

Iako redak entitet, CNS-MM predstavlja veliki dijagnostički, klinički i terapijski izazov koji iziskuje dalja ispitivanja u cilju produžetka preživljavanja obolelih.

Sukob interesa: Nije prijavljen.

25 months), compared to patients with leptomeningeal infiltration (mOS 6 months), had a better survival time [6]. In our patients, the mOS is 34 months, while the mOS from the moment of diagnosis of CNS involvement is 22.5 months, which correlates with the survival data of patients who did not have leptomeningeal infiltration.

Given the low incidence of CNS involvement, but also the aggressive nature of its rapid progression, it is necessary to evaluate each new neurological symptom in detail. The neurotoxicity of systemic therapy is a particular differential diagnostic challenge. In our patient, in whom CNS involvement occurred during the relapse of disease, the neurological manifestation could also correspond to the neurotoxicity of the administered therapy. Several cases of the development of progressive multifocal leukoencephalopathy (PML) during the administration of daratumumab have been described in literature [21]. The most common neurotoxicity of proteasome inhibitors and immunomodulators is peripheral neuropathy [26,27], especially during combined administration. Thrombocytopenia and prothrombogenic states caused by immunomodulators can, in rare cases, be directly related to stroke symptomatology [28].

CONCLUSION

Although a rare entity, CNS-MM represents a major diagnostic, clinical, and therapeutic challenge that requires further investigation for the purpose of prolonging the survival time of patients.

Conflict of interest: None declared.

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