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Case Report

Long Term Follow-Up of a Waldenström's Macroglobulinemia Patient Presenting Bing-Neel Syndrome for the Last Eighteen Years

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Abstract

Waldenström's Macroglobulinemia (WM) is a rare lymphoproliferative disorder that presents a wide range of peculiar clinical manifestations; among them Bing-Neel Syndrome (BNS), concerning infiltration of the Central Nervous System (CNS), is extremely rare and was considered as carrying an adverse prognosis.

We present here a 45-year-old woman diagnosed with WM that developed BNS while being in remission. She received rituximab intrathecally, producing complete resolution of leptomeningeal disease, lasting for 3 years. She subsequently relapsed several times locally and generally, developing lymphadenopathy and retroperitoneal mass that was also thought of adverse prognosis. She received various treatments and finally, in 2014, a Bruton's tyrosine kinase inhibitor, Ibrutinib and achieved a remarkable improvement of her clinical status and a stability of imaging status, without entering complete remission although serum IgM is undetectable, and BM is disease free. She is still under the same treatment and in good clinical condition at present. Concluding, Bruton's tyrosine kinase inhibitors very effectively control rare WM manifestations such as BNS and retroperitoneal disease.

INTRODUCTION

WM is an indolent B-cell lymphoma that belongs to the lymphoplasmacytic lymphoma (LPL) subtype and is characterized by bone marrow (BM) infiltration by lymphoplasmacytes accompanied by a circulating monoclonal IgM protein [1,2]. It is a rare disease, mainly affecting the elderly population with a median age of diagnosis of 68 years.

WM can present with a variety of symptoms, but 25-40% of patients are asymptomatic at diagnosis, and they do not need immediate treatment. The remaining patients present with manifestations attributed to the lymphoma (lymphadenopathy, B symptoms, splenomegaly, hepatomegaly), to BM infiltration (anemia, leukopenia, thrombocytopenia), or to the secreted IgM paraprotein (hyperviscosity syndrome, cryoglobulinemia, autoimmune hemolytic anemia, peripheral neuropathy, autoimmune thrombopenic porphyra, and other).

Bing-Neel Syndrome (BNS) is a very rare manifestation of WM, characterized by infiltration of the CNS by lymphoplasmacytes; it can present any time during WM course, and it presents with various neurological symptoms [2-4].

We herein report a case of Bing-Neel Syndrome with a very long follow up.

CASE PRESENTATION

The medical files of a 45-year-old woman diagnosed with WM in 2001 were retrieved after her informed consent. The patient had a medical history of beta-thalassemia trait, hypothyroidism and atypical arthralgias for the past few months. She consulted us because of fatigue. Laboratory blood tests revealed microcytic anemia (hematocrit of 32%), elevated ESR (115mm, with upper normal limit of 18), elevated total serum proteins (10.5 mg/dl, with upper normal limit of 8,2 mg/dl). Quantitative immunoglobulin measurement and immunofixation revealed a

monoclonal IgM-kappa of 3260 mg/dl (normal range: 40- 230 mg/dl). CT-scans of the chest and abdomen showed small (max-diameter below 1 cm) axillary and para-aortic lymph nodes. Bone marrow biopsy showed 85% lymphoplasmacytic infiltration. She was initially treated with chlorambucil and rituximab and achieved complete response (CR).

In February 2006, while still in remission, she presented with two episodes of fainting, numbness and weakness of left upper and lower extremities. Neurological examination revealed left hypesthesia, diminished vibratory sensation in the periphery. Brain CT-scan showed an enhanced signal of the thin meninges in the superior part of the right parietal and frontal lobes and brain MRI revealed right parietal subcortical area involvement (Figure 1).

Lumbar puncture was performed that revealed infiltration of the CSF by lymphoplasmacytes, immunophenotypically consistent with WM, and IgHV gene rearrangement supported the clonality of the B-cell population. An isolated CNS relapse was diagnosed, and she was treated with 8 intrathecal infusions of Rituximab resulting in a complete resolution of the symptoms. At re-assessment, MRI was negative for any disease activity and neurology examination was improved at all sites (Table 1).

In 2009, the patient presented with cervical lymphadenopathy, and underwent 6 cycles of R-CHOP followed by 2 cycles of R-ESHAP, with consecutive hematopoietic stem cells collection in view of autologous stem cell transplantation.

However, in October 2011, during her pre-transplant work-up, she presented with massive cervical lymphadenopathy and was then administered Fludarabine and adjudicative radiation to the cervical area. At re-evaluation, she was in partial remission, with complete resolution of the cervical lymph node swelling.

In November 2013, due to recurrence of her neurological symptoms she underwent a brain MRI which revealed lesions compatible again with BNS. Cerebrospinal fluid was positive for WM cells. The patient underwent 3 intrathecal infusions of Methotrexate and Dexamethasone, and she was subsequently

Table 1: Neurologic assessment at BNS diagnosis and 9 months post treatment initiation

	Initial	9-months
MRC scale	58	60
Hand grip		
Left	46	64
Right	62	76
Two point discrimination		
Left	1[0.5mm]	0
Right	0	0
Vibration threshold index finger		
Left	1	8
Right	5	8
Vibration threshold Malleolus		
Left	1	8
Right	1	8

MRC= Medical Research Council scale for muscle strength

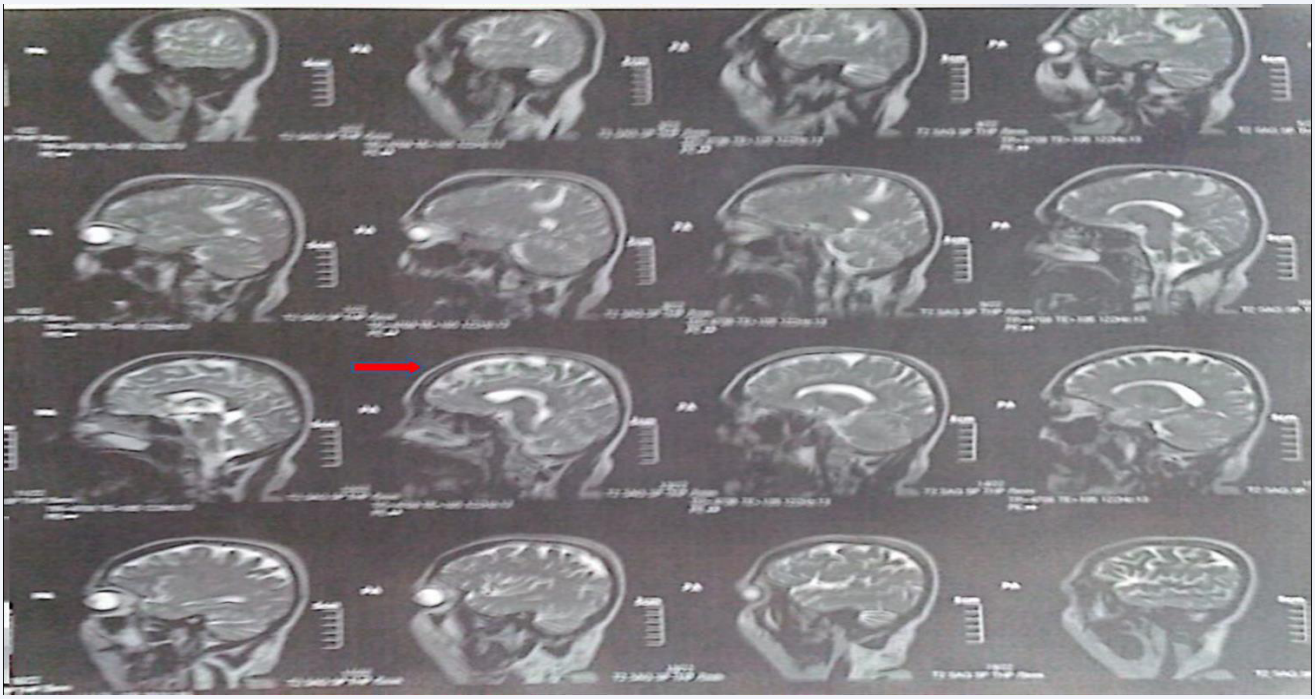

Figure 1 Brain MRI showing high T2 signal intensity in the right parietal subcortical area (red arrow)

re-assessed with brain MRI which demonstrated no response. Therefore, in May 2014, since the patient had previously shown response to intrathecal Rituximab, she received 3 courses, but unfortunately showed no response along with progression at other sites; whole body CT-scans revealed multiple enlarged femoral, inguinal and iliac lymph nodes; involvement of retroperitoneum, gluteal region, and BM was also observed. Inguinal lymph node biopsy was performed which showed findings compatible with LPL. An IgHV gene rearrangement was performed from the FNB of the gluteal mass, the BM and the CSF revealing an identical clone in all compartments (Figure 2).

She received 1 cycle of the Hyper-CVAD chemotherapy regimen but was unable to tolerate it due to excessive hematologic toxicity. In December of 2014, she started Ibrutinib, 140 mg 3 times daily, and at re-evaluation after 2 months with an MRI of the brain and CT-scan of the abdomen, a significant reduction of all lesions was observed. Progressively monoclonal IgM disappeared, and BM biopsy performed 1 year after treatment initiation was disease-free. Since then, she has remained stable, asymptomatic but with residual lesions in the brain and retroperitoneum. She is still under Ibrutinib therapy at a decreased dosage because of neutropenia.

DISCUSSION

Bing-Neel syndrome (BNS) is a rare complication that is encountered in approximately 1% of WM patients, with the exact prevalence being unclear [5,6]. Median time from WM diagnosis to BNS diagnosis is reported to be about 3-4 years [5,7,8]. Nonetheless, BNS can be diagnosed concurrently with WM in about 15-36% [8,6,9], and interestingly it can occur even when WM is in CR [5,6]. BNS is a heterogeneous condition and can present with diverse gradually progressing signs and symptoms, such as visual disturbances, altered mental status, weakness, sensory or motor deficits, gait ataxia, cranial neuropathies, cerebellar dysfunction, seizures, headache, and nausea [5,6,10]. Due to the lack of a pathognomonic clinical picture and its rarity there is often a significant delay between onset of symptoms and diagnosis, with median time being around 4 months, even in patients with established WM [5,6].

Contrast enhanced brain and spine magnetic resonance imaging (MRI) is a useful radiological test for BNS diagnosis. Abnormalities, although not specific for BNS, can be found in up to 80-90% of patients [5,6,10,11]. Most patients present with leptomeningeal involvement (approximately 70%), while dural (37%) and parenchymal (41%), with unifocal or multifocal lesions, involvement is also observed. Some researchers distinguish two separate forms of BNS: the diffuse and tumoral form [6,10,11]. However, parenchymal, and leptomeningeal infiltration can coexist [5,10]. Apart from supporting a BNS diagnosis, MRI is essential for ruling-out other differential diagnoses and opting a possible biopsy site [6].

The gold standard for diagnosis is the histological evidence of CNS tissue infiltration by monoclonal lymphoplasmacytes, immunohistochemically and morphologically resembling LPL [6,11]. However, since brain biopsy is not always feasible due to a non-accessible site or a diffuse leptomeningeal infiltration pattern, a diagnosis can be reached by cerebrospinal fluid (CSF) analysis. The latter can reveal the presence of a clonal B-cell population with light-chain restriction in multicolor flow-cytometry (MFC). More specific molecular studies include PCR assays for IGH gene rearrangement, to establish the clonality of the lymphoid B-cell population, and MYD88 gene L256P mutation. The latter has a high diagnostic value when performed in a BM or peripheral blood specimen, supporting a WM diagnosis. However, in the CSF is also supportive of alternative diagnoses, such as Primary CNS lymphoma [5,6,11]. In addition, presence

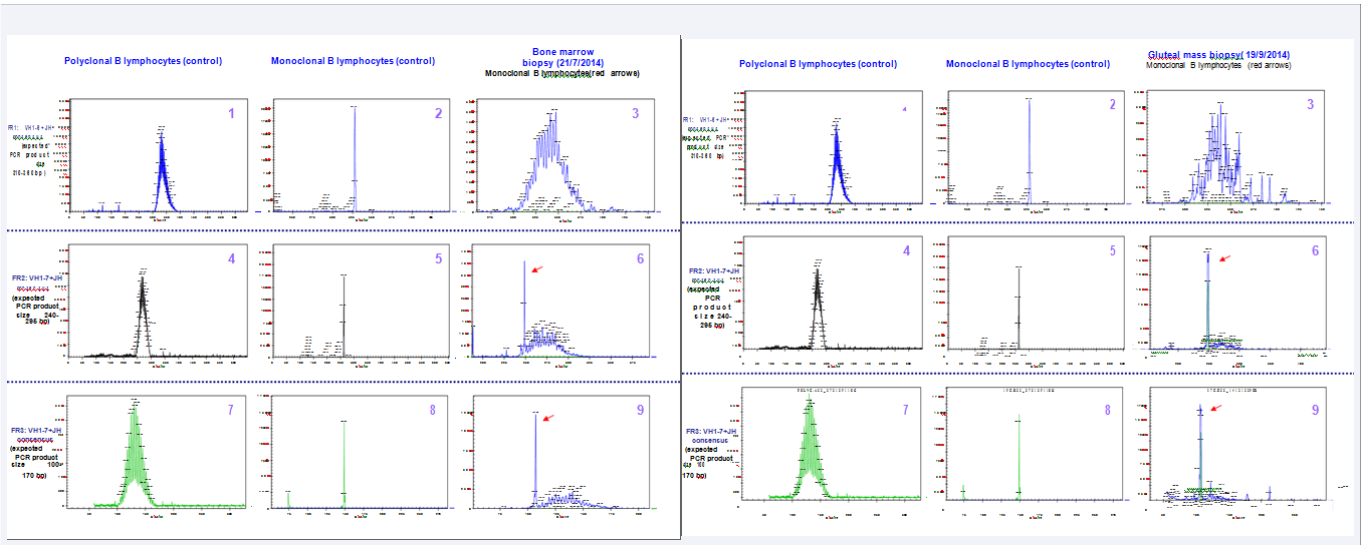

Figure 2 IgHV gene rearrangement: PCR assay revealed an identical clone in the BM and gluteal mass.

of MYD88 L256P mutation in CSF should not be confirmatory of BNS in asymptomatic or low-suspicion patients, since WM small lymphocytes can invade CNS without causing BNS [8].

Our patient was diagnosed with BNS five years after the diagnosis of WM, for which she was treated initially with rituximab IV plus chlorambucil and achieved a CR. She had a radiologic BNS presentation consistent with leptomeningeal disease, without any focal lesion amenable to biopsy. Hence, lumbar puncture was performed that revealed infiltration of the CSF by lymphoplasmacytes, immunophenotypically consistent with WM, and IgHV gene rearrangement supported the clonality of the B-cell population.

Currently, there is a lack of a standardized therapeutic approach for BNS [5,6,8,11,12]. Conventional systemic chemotherapy with known penetration of blood-brain barrier (BBB), such as high-dose methotrexate, high-dose cytarabine, bendamustine and fludarabine, in combination with intrathecal chemotherapy, have been used in BNS, and those regimens are adapted from protocols for lymphomas with primary or secondary CNS infiltration. The response rates for BNS vary and, unfortunately, regimens that incorporate those medications in high doses, lead to severe toxicity that patients with WM/BNS, who tend to be of older age, may not tolerate [6,8].

Rituximab, a humanized murine anti-CD20 IgG monoclonal antibody, has been used systemically in addition to ibrutinib or chemotherapy, when other systemic manifestations of WM exist [12]. However, data show that CNS penetration when used intravenously is questionable [6,8,12,13]. To circumvent this hindrance rituximab has been used since early 2000s intrathecally (IT) in B-cell neoplasms that affect the CNS primarily or secondarily, such as cerebral post-transplant-lymphoproliferative disorder [13], B-NHL with leptomeningeal infiltration [6,14-16] and relapsed CD20-positive B-acute lymphoblastic leukemia [17], with complete regression of symptoms. Interestingly, IT rituximab showed remarkable improvement even in patients who did not respond to systemic plus IT conventional chemotherapy (methotrexate, cytarabine) [13], while showing an additive effect to systemic chemotherapy, allowing dose reductions, and preventing severe drug-induced toxicities [15]. IT rituximab has been used for treatment of BNS, but data are scarce [6,8]. Additionally, responses to IT described are only short-lived, as described in most monotherapy approaches to patients with IT medications only [6].

Our patient's first relapse was an isolated BNS with no evidence of reemergence of monoclonal IgM in serum immunofixation. Subsequently, she was treated with IT infusions of rituximab (25 mg each for 6 consecutive weeks) resulting in a complete radiologic, and symptomatic response along with CSF clearance, that lasted for more than 3 years. There are very few case reports for the use of IT Rituximab in BNS, and as in most regimens that incorporate IT medications only, the responses that are described are brief [6]. In a recent review about the management of BNS, IT Rituximab is suggested only for the relapsed disease or for palliative causes [12]. However, we suggest that IT-rituximab is a viable therapeutic option in isolated BNS (the leptomeningeal form) with no other WM manifestations, especially in patients who are frail and incapable of tolerating intensive conventional chemotherapy regimens or ibrutinib.

Ibrutinib, a Bruton's tyrosine kinase (BTK) inhibitor, has been approved for the treatment of WM, inducing an overall response rate of 91%, dosed at 420 mg once daily [6,7]. Ibrutinib can achieve adequate CSF concentrations and its efficacy has been proven in patients with chronic lymphocytic leukemia and mantle cell lymphoma involving the CNS [7]. In a retrospective multicenter study involving 28 patients with BNS, ibrutinib was used as first-line or salvage treatment, rendering symptomatic and radiologic improvement in 84% and 57% respectively, within 3 months. The estimated 2-year EFS rate was 80%. There is no consensus on the optimal dose, although it is well known that higher ibrutinib doses lead to higher CNS concentrations. However, the authors found no difference in response in higher ibrutinib-dose groups and suggested initiating on 420 mg once daily and escalating to 560 mg if suboptimal improvement is noticed [7].

Our patient's third relapse was generalized, involving the CNS, lymph nodes, retroperitoneum, gluteal region, and BM. A IgHV gene rearrangement was performed from the FNB of the gluteal mass, the BM and the CSF revealing an identical clone in all compartments. She was initiated on 420mg of ibrutinib once daily, and after two cycles a complete resolution of her symptoms and a clearance of CSF from WM clonal lymphoplasmacytes were noted. However, a complete radiological resolution as followed with serial MRI-br was never achieved, with findings improving but never completely disappearing. Consequently, intra-abdominal and retroperitoneal masses decreased in size but were not completely resolved.

WM is an indolent lymphoma, and a physician should aim for disease control rather than disease eradication [6]. In BNS it has been described that 40% of patients have a persistent disease as manifested by MRI-br or/and CSF analysis, but with complete symptoms amelioration, which is the actual goal of treatment, as in WM [6,8,11]. The rationale behind this observation comes in agreement with the well-established observation that most WM patients treated with ibrutinib achieve symptomatic response and disease control, while the BM infiltration and the IgM levels are lowered but not completely vanished. The effect of ibrutinib on both BNS and WM could be attributed to its disease-modulating rather than cytotoxic mechanism of action [7,12]. Notably, in our patient despite the partial response regarding the BNS, her immunofixation became negative during the course with ibrutinib, suggesting that the site of the disease and the dosage may play a role to what grade of response is achieved.

Moreover, in our patient a dose reduction was needed, after approximately one year of treatment, due to adverse reactions (cytopenias). Nonetheless, even at a much lower dose than the one bibliographically needed to attain adequate CSF concentrations,

therapy with ibrutinib continued to provide sufficient disease control, and the patient did not relapse.

Importantly, the generalized relapse of our patient appeared along with a retroperitoneal and a gluteal mass, two sites that are considered extremely rare for WM/LPL. Nonetheless, both the histological examination of the retroperitoneal and the gluteal mass affirmed the LPL diagnosis and the PCR assay for IgHV rearrangement from the gluteal mass and the BM revealed that the neoplastic cells derive from the same clone. There are scarce case reports about WM/LPL involving the aforementioned sites.

Unfortunately, since BNS is a rare complication of an already rare disease such as WM, no established prognostic factors exist [6]. Some case-series report advanced age, number of previous treatments for WM and thrombocytopenia (platelets <100 x10^9/l) as adverse prognostic factors [8,12].

Nonetheless, the median follow-up of patients with BNS including those treated with ibrutinib, ranges from 36 months [9] to 2 years [7], with the largest being 6 years in a study from France [12] and rare case reports of survivals for more than 10 years [5,6].The 3-year overall survival in two recent studies in US and France is estimated at 60% with most deaths happening within 2 years after BNS diagnosis [8]. Our patient is alive after 18 years of her initial BNS diagnosis and after 10 years being on ibrutinib treatment. To our knowledge this is one of the longest follow-ups in general and in the ibrutinib group as well.

CONCLUSION

BNS is a rare manifestation of WM with various clinical and imaging findings, hence physicians should have high clinical suspicion in every WM patient presenting with neurological findings, to avoid any delay in diagnosis. Still there is no consensus on the therapeutic algorithm, although ibrutinib has shown remarkable results in the therapeutic strategy. In our patient, the management of the disease with Ibrutinib was life changing. Lastly, we would like to highlight that IT Rituximab appears to be a viable therapeutic option in selected cases, such as frail patients with isolated leptomeningeal form of the disease.

REFERENCES

1. Kyrtsonis MC, Vassilakopoulos TP, Angelopoulou MK, Siakantaris P, Kontopidou FN, Dimopoulou MN, et al. Waldenström's macro globulinemia: clinical course and prognostic factors in 60 patients. Experience from a single hematology unit. Ann Hematol. 2001; 80: 722-727.
2. Kastritis E, Leblond V, Dimopoulos MA, Kimby E, Staber P, Kersten MJ, et al. Waldenström's macroglobulinaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2018; 29: iv41-iv50.
3. Cabannes-Hamy A, Lemal R, Goldwirt L, Poulain S, Amorim S, Pérignon R, et al. Efficacy of ibrutinib in the treatment of Bing-Neel syndrome. Am J Hematol. 2016; 91: E17-E19.
4. Abdelrahman Nanah, Samer Al Hadidi. Bing-Neel Syndrome: Update on the Diagnosis and Treatment. 2021; 22: E213-E219.
5. Wang W, Lin P. Lymphoplasmacytic lymphoma and Waldenström macroglobulinaemia: clinicopathological features and differential diagnosis. Pathology, 2020; 52: 6-14.
6. Minnema MC, Kimby E, D'Sa S, Fornecker LM, Poulain S, Snijders TJ, et al. Guideline for the diagnosis, treatment and response criteria for Bing-Neel syndrome. Haematologica. 2017; 102: 43-51.
7. Castillo JJ, Itchaki G, Paludo J, Varettoni M, Buske C, Eyre TA, et al. Ibrutinib for the treatment of Bing-Neel syndrome: A multicenter study. Blood. 2019; 133: 299-305.
8. Castillo JJ, D'Sa S, Lunn MP, Minnema MC, Tedeschi A, Lansigan F, et al. Central nervous system involvement by Waldenström macroglobulinaemia (Bing-Neel syndrome): A multi-institutional retrospective study. Br J Haematol. 2016; 172: 709-715.
9. O'Neil DS, Francescone MA, Khan K, Bachir A, O'Connor OA, Sawas A, et al. A Case of Bing–Neel Syndrome Successfully Treated with Ibrutinib. Case Rep Hematol. 2018; 2018: 8573105.
10. Fitsiori A, Fornecker LM, Simon L, Karentzos A, Galanaud D, Outteryck O, et al. Imaging spectrum of Bing–Neel syndrome: how can a radiologist recognise this rare neurological complication of Waldenström's macroglobulinemia? Eur Radiol. 2019; 29: 102-114.
11. Naveed Ahmad JA, Schroeder BA, Yun JPT, Aboulafia DM. Mixed Diffuse and Tumoral Form of Bing-Neel Syndrome Successfully Treated with Ibrutinib. Case Rep Oncol. 2023; 16: 1353-1361.
12. Castillo JJ, Treon SP. How we manage Bing–Neel syndrome. Br J Haematol. 2019; 187: 277-285.
13. van de Glind G, de Graaf S, Klein C, Cornelissen M, Maecker B, Loeffen J. Intrathecal Rituximab Treatment for Pediatric Post-Transplant Lymphoproliferative Disorder of the Central Nervous System. Pediatr Blood Cancer. 2008; 50: 886-888.
14. Antonini G, Cox MC, Montefusco E, Ferrari A, Conte E, Morino S, et al. Intrathecal anti-CD20 antibody: An effective and safe treatment for leptomeningeal lymphoma. J Neurooncol. 2007; 81: 197-199.
15. Liu CY, Teng HW, Lirng JF, Chiou TJ, Chen PM, Hsiao LT. Sustained remission and long-term survival of secondary central nervous system involvement by aggressive B-cell lymphoma after combination treatment of systemic high-dose chemotherapy and intrathecal rituximab. Leuk Lymphoma. 2008; 49: 2018-2021.
16. Luis Villelaa b, Mauricio Garcíaa, Rocío Caballeroa, Borbolla-Escobozab JR, Bolaños-Meade J. Rapid complete response using intrathecal rituximab in a patient with leptomeningeal lymphomatosis due to mantle cell lymphoma. Anticancer Drugs. 2016; 19: 917-920.
17. Jaime-Pérez JC, Rodríguez-Romo LN, González-Llano O, Chapa-Rodríguez A, Gómez-Almaguer D. Effectiveness of intrathecal rituximab in patients with acute lymphoblastic leukaemia relapsed to the CNS and resistant to conventional therapy. Br J Haematol. 2009; 144: 794-795.