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Case Report and Review

Intraventricular treatment of secondary central nervous system lymphoma – Case study and literature overview

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ABSTRACT

Secondary nervous system lymphoma (SCNSL) is a rare extranodal form of non-Hodgkin lymphoma (NHL). This applies to a particular form of lymphoma that does not originally derive from the central nervous system (CNS); it can be both an isolated form of relapse or a systemic part of disease progression. Due to poor prognosis and a lack of established algorithms of therapeutic procedures, it is a big challenge for physicians from many specializations. In our study, we present an interesting case of a patient with a relapsed form of SCNSL for whom a unique form of treatment was used – intraventricular administration of rituximab and methotrexate.

1. Introduction

Lymphomas of central nervous system (CNS) both in a primary (PCNSL) and secondary form (SCNSL) are a rarely diagnosed extranodal location of non-Hodgkin lymphomas (NHL) usually with poor prognosis. SCNSL is a particular type of lymphoma, which does not initially derive from the CNS; it can present both as an isolated form of relapse or a systemic part of disease progression [1]. SCNSL is usually detected within a few weeks or months after a diagnosis of systemic lymphoma. It affects both the brain and cerebral meninges [2]. PCNSL is treated with chemotherapy based on high doses of methotrexate (MTX) [3].

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The selection of optimal therapy for recurrent and resistant CNS lymphomas, is a particularly difficult challenge and creates many more doubts. In this study, we present a case of a patient with a relapsed form of a secondary CNS lymphoma for whom a unique form of treatment was used – intraventricular administration of rituximab and methotrexate.

2. Case presentation

In March 2013, diffuse large B-cell lymphoma (DLBCL, NOS; CD20+, CD5+/−, CD10+, BCL2+, BCL6+, MUM1−/CD43-, Ki-67++ approx. 50% of cells) at stage IV B was diagnosed in a 74-year-old man on the basis of a histological examination of a pancreas sample and the surrounding lymph nodes. A total of 8 cycles of R-CHOP immunochemotherapy was ordered. In result complete remission (CR) was obtained. At the same time, the patient was receiving a hormone therapy due to prostate cancer. In September 2015 (with CR lasting 21 months) an isolated recurrence of lymphoma in the CNS, affecting the meninges and ependyma, was discovered and radiotherapy was started. A dose of 3000 cGy radiation was used on the brain and the medulla oblongata. A check-up PET examination revealed complete regression of lymphomatous lesions in the CNS and no relapse of the tumour of lymphoma in other parts of the body. After a 4-month observation, the patient's general condition deteriorated, and progressive psychomotor slow-down and memory disorders were observed. After another two months, a generalised epileptic seizure occurred. In April 2016 an MRI scan of the head showed a lymphomatous infiltration of the brain, the lateral ventricular walls, the septum pellucidum and the 3rd ventricle (Fig. 1 presents contrast enhancement of the tissue infiltrating the right lateral ventricle wall). An examination of the cerebrospinal fluid (CSF) did not reveal the presence of lymphomatous cells. The test for human immunodeficiency virus (HIV) was negative, however the test for the Epstein–Barr virus (EBV) was not performed.

The patient was qualified for the Ommaya reservoir implantation to administer chemotherapy. Such a decision was made due to the patient's advanced age, general condition (ECOG-3) and numerous co-existing diseases (prostate cancer, distal pancreatic resection in case history, degenerative spine disease, hypothyroidism, hypertension, diabetes). At the same time the patient did not consent to systemic chemotherapy. The treatment regimen consisted of simultaneous administration of rituximab (25 mg) and methotrexate (10 mg) twice a week for 4 weeks (8 doses in total). During the entire uneventful course of the intraventricular immuno-chemotherapy, steroid medications were not used, however considerable improvement in the psychomotor condition of the patient occurred. After therapy completion, an MRI check-up revealed considerable regression of changes in the CNS (Fig. 2). On treatment cycle end the patient was transferred to the Long-Term Care Unit. Unfortunately, he did not consent to further treatment. The documented period of the stable neurological state confirmed with CT was 7 months. Information about the later patient's medical history is not known.

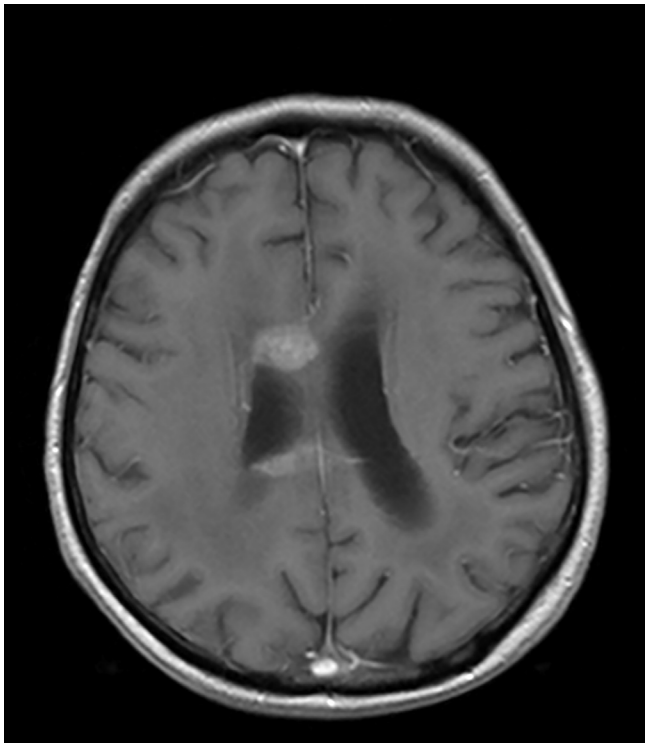

Fig. 1 – T1-weighted contrast-enhanced MR imaging presents contrast enhancement of the tissue infiltrating the right lateral ventricle wall before treatment.

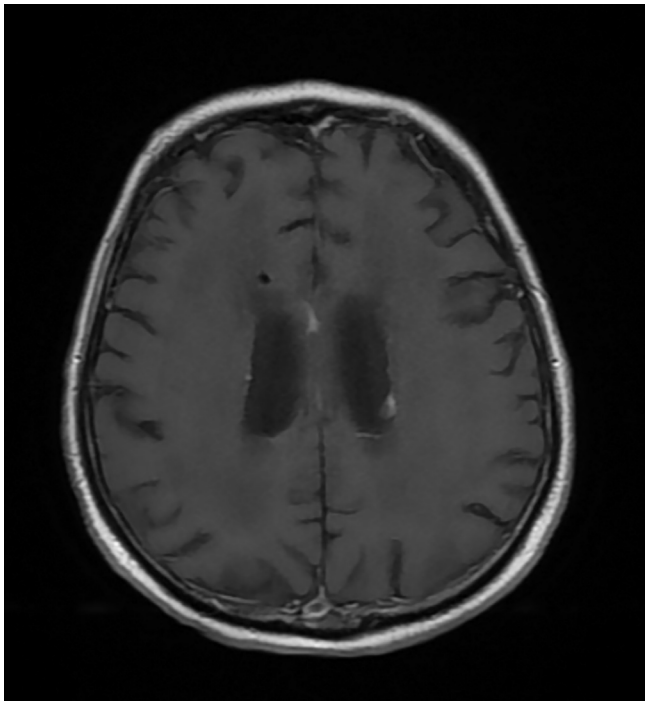

Fig. 2 – T1-weighted contrast-enhanced MR imaging presents radical regression of infiltrating changes in the right lateral ventricle wall after treatment.

3. Discussion

Diffuse large B-cell lymphomas (DLBCL) are one of the most often diagnosed types of non-Hodgkin lymphomas [4]. The use of regimens containing rituximab, vincristine, cyclophosphamide and prednison (R-CHOP) has made it possible to cure 50–60% of patients [5]. However, therapy of subjects with recurrent disease, especially affecting the central nervous system, is still a big problem. It is a particularly unfavourable location in terms of prognosis. The overall median survival time is 3–6 months [6]. The incidence of the isolated CNS recurrence in course of DLBCL is diagnosed in 1.1–10.4% of cases. Such a considerable discrepancy between the data probably results from the high diversity of presented groups and a lack of uniform methods assessing changes in the CNS [2,7–13]. The most frequently recommended and, at the same time, most modern and most sensitive diagnostic methods include magnetic resonance imaging and fluorescence-activated cell sorting analysis of CSF. Their use makes it possible to detect CNS lymphomatous infiltration in cases where it would not be possible with the use of traditional methods [14,15].

It was reported that an introduction of rituximab into treatment regimens had a significant, advantageous effect on reducing the number of the recurrences of the diseases in the CNS [9,16]. This is, however, not confirmed by other researchers [6,17]. Rituximab is a monoclonal antibody characterised by poor penetration of the blood–brain barrier. After intravenous administration, its concentration in the cerebrospinal fluid reaches only 0.1% of that in the serum [18]. However, it was also shown that it could be effective during the first week of therapy when the blood–brain is probably destroyed by actively growing tumour tissues [19]. The problem of poor permeation to the CNS also applies to other drugs included into the CHOP regimen. This may account for the occurrence of isolated recurrences of lymphoma in the CNS with a simultaneous lack of symptoms of the systemic disease [20].

The prognosis for patients with both PCNSL and the secondary form of the CNS disease improved significantly when, at the end of the 1970s, Ervin et al. proved the effectiveness of intravenous treatment with large doses of methotrexate [21]. It was also established that primary diffuse large B-cell lymphomas situated in the CNS are over three times more sensitive to Mtx as compared to systemic lymphomas (the mechanism of this phenomenon is unknown as yet) [22].

In the presented case report an infiltration in the CNS was detected first time at 21 month after lymphoma diagnosis. The median time of CNS recurrence in an analogical group of patients is about 7.2 months. Such a short time of relapse may be connected with a subclinical presence of abnormalities in the CNS at the moment when DLBCL is diagnosed and a lack of sufficient penetration of the CNS by drugs of standard therapeutic regiments [23].

The treatment of lymphoma recurrence in the CNS is a particularly difficult challenge. There are no uniform diagnostic and therapeutic algorithms, thus the individual decisions considering numerous factors, such as the patient's age and clinical status, previous treatment and co-existing diseases, should be made. Research analysis in this field, which is often retrospective and includes variable groups of patients, does not provide any useful suggestion. So regimens used in primary cerebral lymphomas therapy are quite often used in the treatment of secondary CNS lymphomas as well. However, their effectiveness is considerably lower [24]. CNS lymphomas are highly sensitive to whole brain radiation therapy (WBRT), that, however, has a lot of harmful side-effects. The median overall survival time of patients, for whom it was the only one type of treatment, was about 11 months, and the disease recurred in over a half of the patients in the irradiated area. The most frequent complications include: urinary incontinence as well as walking and memory disorders. They occur mostly in patients who are over 60 years old, usually a year after the end of radiotherapy, and they significantly reduce the quality of their life [25].

Korefel et al., in the phase II prospective study, pointed to the possibility of the application of systemic, high-dose chemotherapy, combined with autologous stem-cell transplantation (ASCT) in SCNSL in group of patients below 65 years of age. This could give the chance of an approximate 2-year disease control period in approx. 50% of patients [26].

A combination of rituximab and high-dose sequential chemotherapy and ASCT constitutes an interesting treatment option. Ferreri et al. demonstrated the high effectiveness of this type of treatment in the group of patients between 18 and 70 years of age. Particular attention should be paid to the fact that 2/3 of patients who underwent ASCT and remained in CR for a 5-year observation period [27]. High-dose chemotherapy with ASCT is used to intensify the treatment and to break the resistance to treatment [28].

The recent comprehensive genomic analyses served as a basis for attempts to apply nivolumab (human programmed death receptor-1 blocking antibody) in patients with a resistant/recurrent form of PCNSL [29]. Experimental treatment with ibrutinib [30], lenalidomid combined with rituximab [31], and anti-CD19 CAR T cells, is a very promising option, too [32].

Intraventricular or intrathecal administration of cytostatics combined with systemic chemotherapy was included in treatment regimens. Stereotactic placement of Ommaya reservoir, provides such an opportunity [33]. One of the best-known systems using this method is the Bonn multidrug regimen, assessed by Pels et al. in the first line therapy in 65 PCNSL patients. The authors obtained a high percentage of responses – 71% (61% CR and 10% PR). The median overall survival in the group over 60 years of age was 34 months; it was not achieved in the group of younger patients [34].

In the first prospective phase I study, Rubinstein et al. analysed the effectiveness and safety of intraventricular immunochemotherapy (rituximab + methotrexate) in patients with a recurrent or resistant form of PCNSL. This study was established as a response to the need for looking for the new methods of treatment of this highly selected group of patients with an extremely poor prognosis. In 75%, total eradication of lymphoma cells from the CSF was achieved and in 43% of patients that was also applied to the brain. Regression of lymphomatous lesions was found in the corpus callosum and in the basal ganglia, structures that are thought to be difficult to reach as for cytostatic drugs solved in the cerebral spinal fluid. Pharmacokinetic tests performed in this study revealed

an advantageous profile of rituximab action when combined with Mtx. The administration of both drugs slowed down the elimination of the monoclonal antibody probably caused by a change of the CSF flow. This promotes maintaining constant concentrations of this protein, which is of great importance in the prevention of rituximab resistance [24].

The intraventricular dose of rituximab (25 mg) resulted from previous experiments by Rubinstein et al. The authors assessed the effectiveness of rituximab monotherapy with intraventricular administration through the Ommaya reservoir in a group of 10 patients with recurrent, primary or secondary cerebral lymphomas. The drug was initially used once a week (during the first week) and next twice a week (for the next four weeks). From the administered doses (10, 25 and 50 mg), after the subsequent re-assessment of the patient's condition, 10 and 25 mg proved to be the most effective and safest doses [18]. A subsequent study by Rubinstein included 14 patients after a few lines of treatment (including 11 with DLBCL) with a recurrent/resistant form of CNS lymphoma. A secondary form of CNS lymphoma was found in eight of them, and WBRT had been provided previously to 2 of them [24].

In the presented case the decision on the use of intraventricular injections of rituximab and methotrexate resulted from an advanced age of patient, numerous co-existing diseases (including cancer), poor general condition and patient's decision. No symptoms of intolerance were observed during the therapy and a surprising considerable improvement in the patient's neurological state was achieved, which was confirmed by MRI scans. In our opinion, the efficacy of intraventricular chemotherapy results from the direct effects that drugs in CSF have had on the lesions infiltrating the lateral ventricle lining. Grossman and co-authors' research assessing the efficacy of intraventricular methotrexate administration suggest that high drug concentration may only be expected in the immediate vicinity of the chambers, while the other areas of the brain may reach the drug at much lower concentrations [35].

It is possible, however, that even a small dose of the drug might be effective, at least in some cases, especially when the injections are repeated.

In patients with recurrent/refractory CNS lymphoma who did not qualify for intensive chemotherapy, attempts were made to use temsirolimus monotherapy. Unfortunately, despite demonstrating the activity of the drug in the study group, the effect was short-lived (median progression-free survival was 2.1 months) [36]. A retrospective analysis of Wang et al. regarding PCNSL patients presented a beneficial effect of using high-dose methotrexate plus temozolamide. The authors also suggest the possibility of undertaking an analogous therapy in patients with more advanced age and poor general condition. However, all these proposals require further research [37].

4. Summary

Intraventricular immunochemotherapy is a safe and effective therapeutic option, sometimes the only available one, for patients with an isolated recurrence of CNS lymphoma. It is mostly targeted at patients in poor general condition who cannot receive intensive chemotherapy. Due to the fact that so far it has been used in single cases only, a lot of questions still need to be answered. This applies the possibility of a potential increase in the rituximab and methotrexate doses or the possibility of increasing a number of treatment cycles used. The promising results, which have been presented in our study, should encourage further research on this issue.

Conflict of interest

None declared.

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