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Review article

Primary central nervous system lymphoma as a neurosurgical problem

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ABSTRACT

Primary central nervous system lymphoma (PCNSL) comprises around 3–5% of primary central nervous system (CNS) tumours and around 1% of all non-Hodgkin lymphoma (NHL). Diffuse large B-cell lymphoma (DLBCL) is the most common histological type. High effectiveness of chemo- and radiotherapy for PCNSL regrettably does not eliminate significant risks of recurrence for CNS tumours. That results in higher interest in other treatment options, including surgical procedures. PCNSL remains in the scope of interest for many specialists and neurosurgeons seem to play a more important role.

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1. Introduction

Primary central nervous system lymphoma (PCNSL) is a rare type of non-Hodgkin lymphoma (NHL). It comprises around 3–5% of primary central nervous system (CNS) tumours and around 1% of all NHL [1]. In more than 90% of cases it is diffuse large B-cell lymphoma (DLBCL). T-cell lymphoma or those with lower grade are far less common [2]. Histopathologically PCNSL cannot be differentiated from the systemic form. Significant differences are estimated according to biological, genetic and clinical aspects [3]. Acquired (AIDS) or congenital immunodeficiency syndromes are established risk factors for PCNSL. In case of severe congenital immunity disorders, such as ataxia telangiectasia syndrome or Wiskott-Aldrich

syndrome, the risk reaches around 4%. The frequency of post-transplant lymphoproliferative disorders (PTLD) localised in CNS after kidney, heart or lung transplantation is estimated to be 1–7%. Infections with Epstein-Barr virus (EBV) or iatrogenic T-lymphocyte dysfunctions play a key role in the pathogenesis of these processes [3]. The answer to the question on how lymphoma develops in areas normally free from lymphoid tissue has not been clarified so far. One of the theories suggests “capturing” lymphocytes by CNS during an inflammatory process and their further neoplastic transformation [4,5]. Lu et al. reported on a case of a 44-year-old female patient who was diagnosed with PCNSL in the area where active inflammatory process was detected 2.5 years previously. According to the authors, neuroinfection may precede or

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accompany primary brain lymphoma. Both may be very similar, especially in the initial stadium, which may lead to diagnostic problems or make treatment difficult. Inflammatory processes usually cause demyelination or damage to the nervous tissue, which differs considerably from PCNSL during histological evaluation. That fact does not exclude hypotheses which indicate the importance of inflammatory foci as the first “immunological” response to developing tumours. However, such suggestions need confirmation in further studies [6]. Despite many controversies, chemo- and radiotherapy is the most commonly recommended first-line treatment for PCNSL. Methotrexate (Mtx) is an important agent in monotherapy or in conjunction with other cytostatic drugs. Both the range of dose (1–8 g/m²) and its efficacy are noticeable. Interestingly, susceptibility to Mtx in PCNSL has been shown to be almost three times higher than in systemic lymphoma [7].

2. Diagnostics

In patients with severe neurological symptoms, after performing computed tomography (CT) without contrast medium, a hypodense lesion may be detected, which may resemble ischaemic areas. Magnetic resonance imaging (MRI) is the diagnostic tool to approximate the appropriate diagnosis. PCNSL is iso-hypointensive in T1-weighted images and shows hyperintensive signal in T2-weighted images. Administration of contrast medium gives homogenous enhancement, however sometimes hypointensive necrosis is seen. In order to differentiate other brain lesions [other primary or metastatic tumours, neurosarcoidosis, infections] one should consider extending diagnostics with positron emission tomography (PET), single-photon emission computed tomography (SPECT), MRI spectroscopy (MRS) or perfusion MRI [8]. These may facilitate differentiation between PCNSL and glioma, which is the most common CNS tumour in differential diagnosis. In the case of PCNSL there is less damage of the blood–brain barrier, more vascular permeability, lower central blood volume (CBV) and higher leakage coefficient when compared to glioma [9]. This information may be helpful to undertake the adequate surgical strategy [biopsy/resection]. However the final diagnosis of PCNSL requires histopathological evaluation of tissue samples. Since collecting samples is repeatedly connected with risk of complications, new alternative methods to reach the specific diagnosis emerge. One of them is the examination of cerebrospinal fluid (CSF), whenever it is safe to perform a lumbar puncture. Cytological, immunophenotype or genetical evaluation is available. Detection of lymphoid cells in CSF practically eliminates the necessity to perform biopsy [10]. However, it should be remembered that these cells are detected only in 1/3 of cases and “negative” results of CSF examination do not rule out PCNSL. Reports on evaluation of miRNA [non-coding RNA molecules, regulating other gene expressions] from CSF have shown lately. In particular, they concern *miR-21*, *mir-19b* and *miR-92a*, whose specificity for PCNSL reached 96.7% [11].

In order to confirm the primary lymphoma location in CNS, complex examination of the patient should be performed. It consists of full blood count, blood biochemistry [kidney and liver function tests, LDH concentration] and serology (HIV), full

eye examination, CSF evaluation. The following are required: brain MRI; CT of neck, chest, abdomen and pelvis; bilateral trepanobiopsy. Testicular ultrasound examination is recommended, especially in older men and in younger men whenever there are abnormalities in physical examination.

3. Steroid therapy

Immunosuppressive and cytostatic effect of corticosteroids on neoplastic cells is used in treating lymphoma. Their role is shown to be essential in the case of PCNSL, however many controversies of their application are emphasised. First effects are usually present after 2–3 days (dexamethasone 8–32 mg/day) and mainly involve oedema reduction, which gives temporary neurological stability. Uncommonly observed complete response (CR) or partial response (PR) of lymphoma lesion may appear as soon as within a few hours. However, it is most commonly expected after at least 10 days. The percentage of patients with a possible reaction of this type is estimated to be 15% and 25%, respectively [12]. Discontinuation of corticosteroid therapy is always connected with a real and extremely possible risk of recurrence at different times. One of the longest remission periods [6.5 years] was reported by Herrlinger et al. [13]. Unfortunately, resumption of treatment does not guarantee success. The maintenance of obtained partial or complete remission is not possible even with permanent corticosteroid therapy. No response to treatment or its considerable reduction results from a few reasons. One of them may be clonal evolution of lymphoid cells, resistant to the drug effect. This resistance may result from both low expression of glucocorticoid receptors [14] and high expression of gene *bcl-2* – responsible for apoptosis processes [15]. Önder et al. reported on interesting results when evaluating the influence of pre-therapy with corticosteroids on histopathological results of stereotactic biopsy samples in PCNSL patients. It turned out that reaching the diagnosis was trouble-free only in less than half patients (48%). However, atypical changes of lymphoid cells were detected in all the other cases, which caused problems in reaching the adequate diagnosis [16]. Histopathological pictures may sometimes suggest an inflammatory process. Areas of demyelination and T-cell infiltrations are occasionally observed [17]. Thus Patrick et al. suggest discontinuation of corticosteroids 7–10 days prior to elective biopsy [18]. Corticosteroids are also reported to have an unfavourable effect during administration of cytostatic drugs by “tightening” the blood–brain barrier. In that manner they are thought to decrease penetration of cytostatic drugs to the brain tissue [17]. On the other hand however, some researchers report on potential prognostic importance of the initial reaction to steroids. A retrospective analysis of 57 PCNSL patients proved that regression of radiological lesions and clinical improvement have a significantly beneficial influence on overall survival [19]. Adequate “radiological” response to corticosteroid therapy together with MRI and FDG-PET, according to Yamaguchi et al., may be used as an alternative method to diagnose PCNSL. It involves lesions located in deep brain structures, for which surgical treatment is connected with high risk of complications [20].

4. Intraventricular treatment

Cerebrospinal fluid is probably a specific reservoir of lymphoid cells in some PCNSL patients. Therefore, intraventricular or intrathecal injections of cytostatic drugs combined with systemic chemotherapy are commonly placed in many therapy protocols. It is possible thanks to an Ommaya reservoir which may be implanted already during stereotactic biopsy [21]. One of the well-known regimens is Boston multidrug regimen used by Pels et al. in 65 PCNSL patients. The authors reported on high 71% response rate (61% CR and 10% PR). Overall median survival (OS) was 34 months for patients older than 60 years and was not reached for younger patients. Infectious complications were observed in 19% cases. Their presence is explained by immunodeficiencies due to steroid therapy and myelosuppression due to cytostatic drugs. Also frequent (according to the protocol) administration of drugs via the reservoir plays an important role [22]. Rubinstein et al. in the first prospective phase I trial evaluated the efficacy and safety of intraventricular immunochemotherapy with rituximab and methotrexate in patients with recurrent or drug-resistant PCNSL. This trial was the answer to search for new treatment modalities of this highly selected group of patients with an extremely unfavourable prognosis. In 75% of patients complete eradication of lymphoid cells from CSF was observed, and in 43% it also involved the brain. Regression of lymphoma lesions was noted in corpus callosum and basal ganglia, which were the structures previously thought to be hard to reach for cytostatic drugs dissolved in CSF. The authors also suggest that concomitant administration of rituximab with Mtx delays elimination of rituximab from CSF. A short half-life of monoclonal antibody is thought to be one of the main reasons for resistance to intraventricular rituximab injections [which usually appears after 1–3 months of treatment]. This probably leads to evolution of drug-resistant clone of lymphoid cells [23].

Rituximab is a murine/human chimeric anti-CD20 monoclonal antibody, specific for B cell line. It shows high activity in treating systemic diffuse large B-cell lymphoma [24]. However, the concentration of rituximab in CSF reaches only around 1% of its serum concentration after intravenous injection [25]. A reasonable explanation for occasional usage of this antibody in induction therapy for PCNSL is a severe damage of the blood–brain barrier in the initial phase of the disease [26].

5. Stereotactic radiosurgery

Primary lymphoma of CNS is characteristic for its high susceptibility to radiotherapy. Ever since its first introduction in early sixties, mainly as the whole-brain radiation therapy [WBRT], it has been a permanent element of many therapeutic protocols. Currently it is known that when applied alone WBRT has many limitations which result from its inadequate efficacy [overall median survival was a little more than 11 months, with recurrent disease in the field of radiation in more than half of patients] [27] and from longterm harmful effects of radiation. Even though their character is known, the

mechanism of neurotoxicity is still questionable. Possible explanations include oxidative stress, oligodendrocyte damage, neurocyte stem cell damage, demyelination or vasculopathy [28]. At the same time it is known that CNS damage degree depends mainly on cumulative total radiation dose [29]. Stereotactic radiosurgery (SRS) is a surgical technique which uses a single, localised, high dose of ionising radiation, with a maximal protection of healthy tissues [30]. According to many authors, SRS has many advantages. Among them is the possibility to perform it in a short period of time [usually one day] and to repeat it when needed. It gives an opportunity to apply a high dose of radiation in locations which are inaccessible for neurosurgery. SRS is not in conflict with systemic chemotherapy, and sometimes it may be the only alternative form of treatment in patients who may not be treated with cytostatic drugs due to multi-organ damages [31]. The idea of applying SRS was presented in a few retrospective studies. The attempts involved both primary and recurrent PCNSL. Sakamoto et al. presented results of treatment in 9 patients who were diagnosed with recurrent CNS lymphoma (both single and multiple neoplastic lesions). All of them underwent WBRT before. The percentage of response (CR + PR) was 87%. Overall median survival and progression free survival (PFS) was 7.7 and 3.7 months, respectively. At the same time it has been proven that OS is significantly longer with prior application of systemic chemotherapy in comparison to patients with no cytostatic treatment (median 5.9 vs. 13.0 months) [32]. Kenai et al. treated a significantly larger group of 22 patients. Altogether 48, mainly recurrent, lymphoma lesions were treated with Gamma Knife Surgery (GKS), which resulted in significant reduction or complete regression of lesions. The authors emphasised high efficacy [100% response] and safety of the therapy. They did not observe progression or recurrence of lymphoma in the primary site over the mean period of 19.4 months. Newly appearing neoplastic foci still reacted well to GKS. Median OS was 38 months [33]. Studies carried out by Hirono et al. have an innovative character, since they attempt to combine SRS with high-dose methotrexate (HD-Mtx) as first-line therapy in patients with newly diagnosed PCNSL. SRS was supposed to replace WBRT in this case and to complement the activity of HD-Mtx at the same time. From 51 patients, radiosurgery was finally applied in 20 people due to residual or recurrent lymphoma changes. Median OS was 52 months with no significant adverse effects [34]. The role of SRS in treating PCNSL is a subject of many discussions. However, it is not questionable for other recurrent brain tumours, such as gliomas, meningiomas or metastatic tumours [35–38]. Its efficacy evaluated in the aspect of overall survival depends on many factors. Some of the particularly include the radiation dose and clinical status of patients before treatment, described by Karnofsky scale. It also seems that SRS is a therapeutic modality for which “local control” of lymphoma lesions is the main goal [39].

6. Surgical treatment

Despite high efficacy of chemo- and radiotherapy in PCNSL, there is a significant risk of recurrence for neoplastic CNS

changes. It increases the interest for other treatment options, including surgical management. Theoretical assumptions which justify this type of approach point to the possibility of cytoreductive effect and elimination of genetically unstable lymphoid cells that are resistant to cytostatic treatment [40]. One of the core arguments against radical surgical actions is the fact that lymphoma changes in CNS are repeatedly multifocal and practically spread throughout the whole brain. Some authors also suggest the possibility of migration of lymphoid cells to the subarachnoid space during the procedure [41]. Since [according to autopsy studies] lymphoma has no capsule, cases of recurrent CNS lymphoma in areas remote to the primary site were observed [42]. Many scientific papers and protocols of national and international neurosurgical bodies questioned the efficacy of lymphoma resection. Emerging reports did not change those opinions. Sonstein et al. described 5-year overall survival in a PCNSL patient after gross total resection of the lesion and short lasting steroid therapy [43]. Trapella et al. reported on more-than-79-month OS. Radio- and chemotherapy was applied in their patient after gross total tumour resection [44]. Davis et al. presented however the most spectacular case (more-than-twenty-year overall survival) [45]. In a large report Bataille et al. showed results of retrospective studies on 248 PCNSL patients, where one-year overall survival was 56.6% for those after gross total resection, 31.8% for those after non-total resection and 48.6% in those after biopsy [46]. The revision of previous sceptical opinions is based on the results gathered in a randomised phase III study, conducted by the German group G-PCNSL-SG-1, which evaluated the efficacy of WBRT in 526 patients with newly diagnosed PCNSL. One of fairly unexpected (and not included in the study hypotheses) conclusions was longer overall survival and progression free time in the group after gross total or non-total tumour resection in comparison to the patients after biopsy only. At the same time, no significant correlation between the location of lymphoma and OS or PFS was proven. The study may provide the basis for changing the acknowledged standpoint that the scope of neurosurgical procedures has no prognostic value, and – what is more – it may simply suggest that gross total or non-total tumour resection (especially in the case of single tumours) may result in measurable benefits for the patient (providing it does not generate the risk of neurological complications or does not postpone further chemotherapy). Due to the significance of the problem, attempts to define the final importance of scopes of neurosurgical procedures seem to be necessary in prospective clinical trials [47].

7. Summary

Primary central nervous system lymphoma is a problem which requires involvement of different specialists (neurosurgeon, neurologist, histopathologist, haematologist, oncologist). Their good and adequate cooperation results in the final success with improvement of yet not fully satisfying treatment effects. The role of neurosurgeon seems to may have an even greater importance in this process. However, it requires further intensive studies.

Conflict of interest

None declared.

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals.

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