VIA MEDICA

REVIEW ARTICLE

Acta Haematologica Polonica 2021
Number 4, Volume 52, pages 349–354
DOI: 10.5603/AHP.2021.0067
ISSN 0001–5814
e-ISSN 2300–7117

Primary central nervous system lymphoma in neurosurgery

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Abstract

Primary central nervous system lymphoma (PCNSL) most commonly (>95%) constitutes a specific kind of diffuse large B-cell lymphoma, which shows expression of CD20, CD19 and CD79a antigens on its surface and belongs to non-germinal center B-cell-like type (non-GCB). This results from both its limited localization as well as immunophenotypic and molecular features. It frequently has an aggressive clinical course and its prognosis remains highly uncertain.

PCNSL's development in areas normally free from lymphoid tissue has not been adequately explained thus far. PCNSL is usually a solitary lesion (60–70%), with the majority (c.60%) occurring in supratentorial areas, and less frequently in telencephalic nuclei and periventricular areas, corpus callosum, infratentorial structures, spinal cord or orbital cavities. Lymphoid cells can occasionally create diffuse infiltration with no mass effect — a PCNSL variant known as lymphomatosis cerebri. Reported clinical symptoms depend on the localization of the tumor in central nervous system. The most common include: cognitive impairment, behavioral changes, focal neurological deficit and symptoms of increased intracranial pressure. A final diagnosis of PCNSL requires histopathological evaluation of tissue samples obtained usually during a stereotactic biopsy. Identifying lymphoid cells in cerebrospinal fluid may also be sufficient. Chemotherapy combined with radiotherapy is the standard treatment of PCNSL. For many years, surgical treatment has been controversial. This provides constant encouragement to explore effective treatment methods, with neurosurgical involvement waiting to be further defined.

Key words: primary central nervous lymphoma, PCNSL

Acta Haematologica Polonica 2021; 52, 4: 349–354

Introduction

Primary central nervous system lymphoma (PCNSL) is an uncommon extranodal group of non-Hodgkin lymphoma (NHL), with no systemic symptoms. PCNSL constitutes approximately 3% of primary central nervous system (CNS) tumors, and approximately 1% of all non-Hodgkin lymphoma [1, 2]. It is diagnosed at all ages, although it is most common in men aged 60–70 [3]. Histologically PCNSL belongs to a homogenous lymphoma group. Most commonly (>95%) it is a diffuse large B-cell lymphoma (DLBCL). The subtype shows expression of CD20, CD19 and CD79a antigens on its surface and belongs to non-germinal center B-cell-like type (non-GCB) [4–6].

Pathogenesis

PCNSL's development in areas where lymphoid tissue is normally absent has not been adequately explained until now. It has been studied by Deckert et al. Immunohistochemical examinations in PCNSL patients showed no expression of lymphatic vessel endothelial hyaluronan

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Received: 30.04.2021 Accepted: 27.05.2021

receptor 1 (Lyve-1), Prospero homeobox protein 1 (Prox-1) or podoplanin — a protein that shows its expression in lymphatic vessel endothelium and is a remarkable marker of lymphatic vessels to evaluate lymphangiogenesis, especially in neoplasms. The authors also suggest that no connection between PCNSL and the lymphatic system prevents the spread of lymphoma outside CNS [7]. Lymphatic cells tend to remain in CNS, thus lymphatic foci outside its primary location are remarkably infrequent [8]. One of the theories behind PCNSL's pathogenesis suggests the possibility of 'capturing' lymphocytes by central nervous system to inflammatory regions, where the lymphocytes undergo neoplastic transformations [9, 10].

Lu et al. described a 44-year-old female patient who was diagnosed with PCNSL in the region where an active inflammatory process had been first observed 30 months previously. The authors stated that neuroinfection may go ahead of or together with primary brain lymphoma. These can show some similarities (especially at an early stage) and can make diagnosis or treatment difficult. Inflammation typically causes demyelination or damages the nervous tissue and differs remarkably from PCNSL during histological examination. However, that finding does not eliminate the hypotheses indicating the significance of inflammatory foci as the primary 'immunological' reaction to developing neoplasms. Such suggestions require verification in further research [11]. The evidence confirms lymphocyte migration to nervous tissue, which depends on specific and selective interactions between lymphocyte adhesive molecules and endothelial cells in brain vessels [12, 13]. This constitutes a partial explanation for angiocentric growth of PCNSL. In some cases, infiltration of the small and medium blood vessel wall is noted and may result in blood-brain barrier damage. This anomaly allows visualization of the lesion with pathological contrast medium enhancement. Reactive small lymphocytes T and active macrophages are visible in the surrounding of a lymphoma tumor [8]. The possible prognostic importance of angiocentric growth in PCNSL and reactive perivascular lymphocyte T infiltration has been suggested. However, this requires a larger tissue sample than what can be obtained during stereotactic biopsies [14, 15].

Clinical features

PCNSL is usually a solitary lesion (60–70%), with c.60% occurring in supratentorial areas (frontal, temporal, parietal and occipital lobes), and less frequently in telencephalic nuclei and periventricular areas, corpus callosum, infratentorial structures, spinal cord or orbital cavities. In c.15–20% of cases meninges are involved, however the course is usually asymptomatic and diagnosed through anomalies in the cerebrospinal fluid (CSF) [16]. Lymphoid cells may sometimes create diffuse infiltration with no mass effect — a PCNSL variant known as lymphomatosis cerebri [17].

Reported clinical symptoms depend on the localization of the tumor in CNS. The most common include: cognitive impairment, behavioral changes, focal neurological deficit and symptoms of increased intracranial pressure [18].

PCNSL has an aggressive clinical course and is thus important to diagnose promptly. Plain computed tomography (CT) in patients with serious neurological symptoms shows hypodense lesions which may resemble ischemic foci. In order to reach the appropriate diagnosis, one should perform magnetic resonance imaging (MRI). Primary central nervous system lymphoma is either iso- or hypointensive in T1-weighted series and is hyperintensive in T2-weighted scans. Contrast medium shows homogenous enhancement, however hypointensive necrosis is occasionally seen. Further diagnostic means, like MRI spectroscopy (MRS), perfusion MRI, single-photon emission computed tomography (SPECT) or positron emission tomography (PET), should be considered in order to differentiate from infections, other brain tumors (primary, metastatic) or neurosarcoidosis [19]. These diagnostic tools may also help differentiate PCNSL from glioma — the most common central nervous system tumor. Comparing with glioma, PCNSL shows higher leakage coefficient, lower central blood volume (CBV), more vascular permeability, and less damage to the blood-brain barrier [20]. After microscopic studies, Lai et al. proved that MRI scans do not always evaluate the area of lymphoma infiltration in CNS perfectly, since no 'radiological' pathology may be observed, even in T2-weighted images [21]. Adachi et al. [22] suggested that the contrast enhanced regions may only represent a part of the neoplastic process.

The final diagnosis of primary central nervous system lymphoma is set after histopathological examination of tissue samples obtained most frequently during a stereotactic biopsy. Identifying lymphoid cells in cerebrospinal fluid (CSF) may also be sufficient. However, lumbar puncture is not always possible. CSF usually has higher protein concentrations and lymphoid cells are observed only in 10–16% of cases [18]. A recent report on the evaluation of miRNA from CSF has shown that they involve *mir-19bi, miR-21* and *miR-92a* with the specificity of 96.7% for PCNSL [23].

Treatment

Chemotherapy combined with radiotherapy is the standard treatment of PCNSL. For many years, surgical treatment has been controversial. Single examples of long overall survival in PCNSL patients after gross total tumor removal with short-lasting steroid therapy [24, 25] or with radio- and chemotherapy [26] have been reported in the literature. Supporters of surgical resection emphasize the possible cytoreductive effect and eradication of genetically unstable and resistant to cytostatic therapy lymphoid cells [27]. Cytoreduction as an important treatment modality is

applied in the therapy of malignant brain tumors, including gliomas. Apart from remission of the symptomatic mass effect, gross total resection contributes to better oncological control and prolongs overall survival (OS) in certain cases. Correlations between resection range and OS are known from observational studies [28–31]. In 2010, the German group G-PCNSL-SG-1 conducted a randomized phase III study which evaluated the efficacy of WBRT combined with high doses of Mtx in 526 patients with newly diagnosed PCNSL. Apart from the principal study aim, OS and progression-free survival (PFS) were significantly longer in patients who underwent gross total or non-total tumor resection in comparison to the group that only had a biopsy. There was no proof for a significant correlation between the site of lymphoma and PFS or OS [32]. Weller et al. observed similar positive effects of surgical treatment. The extent of procedure (gross total/partial resection) had no significance, however the number of lymphoma foci in CNS proved to be significant for prognosis [33]. Tumor resection combined with chemo- and radiotherapy were an effective treatment modality in PCNSL patients studied by Bellinzona et al. [34]. Unfortunately, those positive results have not been confirmed in our own studies (unpublished data) or in studies by Bataille et al. [35] or Jahr et al. [36]. The main argument against radical surgeries is that lymphoid changes in the central nervous system are multifocal and spread throughout deep brain structures. Autopsy studies showed that lymphoma has no capsule and neoplastic cells practically spread throughout the brain. Patients with recurrent central nervous system lymphoma in locations remote from the primary area have been described [37]. Researchers also indicate that it is possible for lymphoid cells to migrate to the subarachnoid space [38]. The risk of postoperative complications is also regarded as a reason to postpone chemotherapy [35]. However, such opinions are mainly based on data from decades before [39, 40]. Lately, the number of complications caused by neurosurgical or anaesthetic procedures has significantly decreased [41–43]. This is connected with a more frequent use of MRI and other modern technologies of visualizing tumors, as well as with better perioperative care [44, 45].

Cloney et al. [46] showed in their retrospective analysis that the number of complications in PCNSL patients after lymphoma resection was comparable to the number of complications in patients with tumors for which gross total resection is the first line treatment. At the same time, no statistically significant difference has been shown for the risk of complications dependant on the range of procedure (resection/biopsy). According to the authors, age and multiple *loci* mainly in deep brain areas should be indications for biopsy [46]. Partial or gross total resection of a lymphoma tumor seems to be beneficial in patients with symptoms of rapidly increasing intracranial pressure. With the use of modern operative techniques, the resection may contribute to the improvement of general condition, and therefore it may be beneficial for the course of disease and for the possibility of starting intensive chemotherapy. Currently, it is the patient's general condition and age that belong to prognostic factors independent from treatment modality in PCNSL patients [47].

The choice of surgery type is extremely complex. Usually, the choice is made for the patient: 'yes for brain tumour' where resection is the treatment of choice, and 'no for lymphoma', since the diagnosis is set only after histopathology. Potential pre- or intraoperative differentiation between primary lymphoma and other tumors (e.g. glioma) remains in relation to this important unsolved problem as to which surgery modality to choose, and can significantly influence the treatment. Intraoperative cytometric examination creates such possibilities of differentiation. A pioneering study was carried out by Koriyama et al. [48], who used differences in DNA histogram of both tumors.

Corticosteroids play an important role in the treatment of neoplasms in the lymphatic system. Their immunosuppressive and cytostatic effects on neoplastic cells is used. At the same time, controversy regarding their application in PCNSL patients remains. First effects are usually present after 2–3 days and include reduction of brain edema and it leads to temporary clinical stability. Rarely observed total or partial response of lymphoma may appear within a few hours [49].

Discontinuation of corticosteroid therapy is always connected with recurrence which may take place after various times. Herrlinger et al. reported on one of the longest remission times — 6.5 years [50]. Unfortunately, restarting the treatment does not guarantee successful effects. Even with permanent corticosteroid therapy, maintaining the obtained partial or complete remission is impossible. No response to treatment, or its considerable reduction, may be explained by clonal evolution of lymphoma whose cells become resistant to the drug. This resistance may be a result of either low expression of glucocorticoid receptors [51] or high expression of gene *Bcl-2* that plays a role in apoptosis processes [52]. Histopathology examinations of stereotactic biopsy samples in PCNSL patients after pre-therapy with corticosteroids were analyzed by Önder et al. [53] who concluded that reaching the diagnosis was trouble-free only in 48% of patients. In all the other cases, however, atypical changes of lymphoma cells were observed and caused problems in reaching the diagnosis. Histopathological images sometimes suggest an inflammation. Occasionally they show areas of demyelination and T-cell infiltrations [54]. That is why Patrick et al. [55] suggest discontinuing corticosteroids 7–10 days before the elective biopsy. Corticosteroids also decrease infiltration of cytostatic drugs to the brain tissue by 'tightening' the blood-brain barrier [54]. Some researchers have reported

on the possible prognostic significance of the original reaction to steroids. Regression of radiological changes and clinical recovery have a importantly beneficial influence on OS (median 17.9 vs. 5.5 months) according to a retrospective analysis of 57 patients with primary central nervous system lymphoma [56]. Adequate 'radiological' response to corticosteroid therapy-caused PCNSL lesions has led to them being called 'disappearing tumors' or 'ghost tumors'. According to Yamaguchi et al. [57], this phenomenon, alongside MRI and FDG-PET, can be applied as an alternative diagnostic means for PCNSL, especially when lymphoma foci are located in deep brain areas, normally connected with a high risk of complications after surgical treatment. However, one must bear in mind that 'disappearing tumor' is not always an accurate description of PCNSL. Bromberg et al. showed that of 12 such cases, PCNSL was diagnosed only in five. In the remaining cases, a demyelinating disease, stroke, sarcoidosis, or renal carcinoma metastasis were diagnosed [58].

In some patients, a Rickham's reservoir is placed. This gives an opportunity to give cytostatic injections intraventricularly, most commonly combined with systemic chemotherapy. The fact that cerebrospinal fluid in some PCNSL patients is probably a specific reservoir of lymphoid cells justifies such a procedure. In a multidrug Boston regimen, Pels et al. [59] used the possibility to concomitantly treat systematically and intraventricularly as first line therapy in PCNSL patients. Surprisingly good results were noted with response rate of 71% (61% CR and 10% PR). Median OS reached 34 months for patients older than 60 and was not reached in younger groups of patients. The fairly high percentage (19%) of infectious complications should be underscored. Infections were caused by immunodeficiencies due to steroid usage and myelosuppression due to cytostatic agents. Repetitive administration of drugs through the reservoir plays a significant role [59].

Recently, the efficacy of immune- and chemotherapy with rituximab and methotrexate administered intraventricularly has been shown in patients with drug-resistant or recurrent primary central nervous system lymphoma. After intravenous administration, the concentration of rituximab in CSF reaches only 1% of its serum concentration and is caused by high (146 kDa) molecular weight [60]. Rubenstein et al. [61] used intraventricular immunochemotherapy and reported on regression of lymphoid changes in basal ganglia and corpus callosum. In a significant percentage (75%) of cases, total elimination of lymphoid cells from cerebrospinal fluid was observed. Such a good treatment efficacy is explained by a beneficial pharmacokinetic profile with a slower elimination of monoclonal antibody from CSF when methotrexate is given at the same time. This probably plays an important role in decreasing the risk of drug resistance to rituximab [61].

Conclusion

Primary central nervous system lymphoma constitutes a significantly aggressive kind of lymphoma that needs aggressive treatment, with chemo- and radiotherapy still playing the lead role. Neurosurgical treatment in PCNSL patients is not routine; however, it seems that in some clinical conditions it should be considered as part of a broad treatment protocol.

Authors' contributions

All authors: writing manuscript, analysis, final approval.

Conflict of interest

None.

Financial support

None.

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; EU Directive 2010/63/EU for animal experiments; Uniform Requirements for manuscripts submitted to Biomedical journals.

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