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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.

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 Ebstein-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 accompany

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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/m^2) 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].

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