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Primary Central Nervous System Lymphoma in an Immunocompetent Young Woman

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Abstract

Primary central nervous system lymphoma is a rare brain tumor and the most common risk factor is immune system deficiency. This tumor can be seen in normal people however it is mainly seen in an age range of 50-70 years and predominantly in the male gender. The incidence of this disease in different ages is also influenced by race. As reported, at the age below 50-years blacks have had higher overall incidence rates in comparison to whites. Although analysis of CSF and hematologic tests can help diagnosis the only definite diagnosis tool is biopsy. The tumor cell's high susceptibility to corticosteroid-dependent apoptosis. Corticosteroids have not been used before biopsy. The main treatment strategy is high dose methotrexate (HD-MTX) - based chemotherapy and whole brain radiation and surgery is restricted to biopsy for diagnostic purposes only. Here we present a case of a young female without immune deficiency who was diagnosed with primary central nervous system lymphoma.

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Introduction

Primary central nervous system lymphoma (PCNSL) is a rare cerebral tumor (1).The most common risk factor for this disease is an immune deficiency. Therefore, it is usually seen in patients with AIDS and those who receive immunosuppressive drugs. Epstein-Barr virus (EBV) is also highly present among PCNSL patients, suggesting a relationship between EBV tumorigenesis effect and PCNSL (2). However, this tumor is also seen in immunocompetent patients at the age of 50-70 years (3). The most common signs of PCNSL are cognitive disorders, personality change, and disorientation. Cerebellar and brain stem involvement, seizure, and cranial palsy, with lower prevalence, have also been reported (4). Although cerebrospinal fluid (CSF) analysis and hematology tests can help diagnosis (5), the only definite diagnosis tool is biopsy (6). Despite the tumor cells' high susceptibility to apoptosis via corticosteroids (7,8), corticosteroids have not been used for long-term treatment, and their intake has contra-indication before biopsy (6). The main treatment strategy is high-dose methotrexate (HD-MTX)-based chemotherapy and whole-

brain radiation (9), and surgery is restricted to biopsy for diagnostic purposes only (10).

Case report

A 32-year-old woman was admitted to the Shahid Sadoughi hospital in Yazd with headache, cognitive disorder, depression, fever, and weight loss for the past four weeks. The patient had no medical history before the beginning of the disease. At the initial examination, the patient had just fever, and all other vital signs were stable. Her physical examination was normal, and no sign of cutaneous rash, abnormal heart and lung sounds, and hepatosplenomegaly were found. The patient was drowsy, without orientation, with central facial paresthesia, right-sided hemi-paresthesia, generalized hyperreflexia, and positive bilateral Babinski. The results of primary test include CBC = normal, CRP = +, ESR = 48 LFT, electrolytes = normal. The results of CSF sample were as the following: WBC = 4 (100%lymphocyte), glucose = 59, pro = 97. Chest radiography was normal.

Brain MRI showed multiple lesions in the periventricular, corpus callosum, basal ganglia, brain stem (Figure1), and the cervical spine (Figure 2), which in T1 there was iso to hypo-intense and in FLAIR and T2, hyperintense. In DWI, a restrictive pattern was seen in a few of the lesions and, in contrast MRI, some of the lesions were enhanced (Figures 2 and 3).

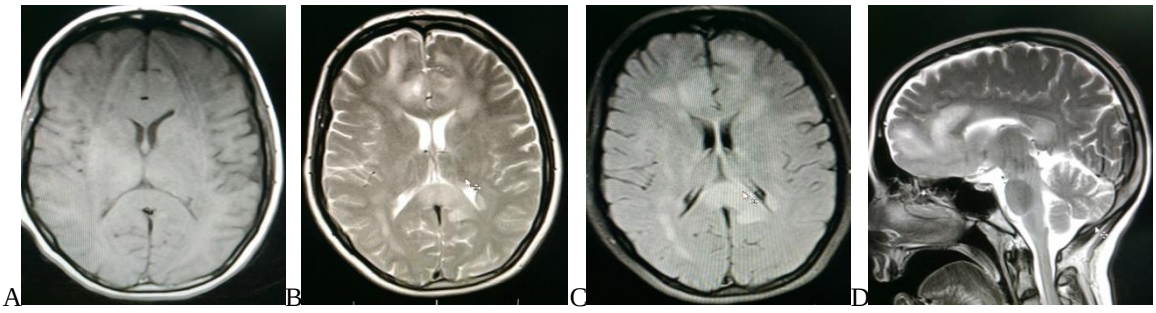


Figure 1. Axial T1 sequences on MRI show iso-intense to hypo-intense (frontal) multiple lesions in the periventricular, centrum semi-oval and corpus callosum (A). Axial T2 and FLAIR sequences on MRI show the same lesions that are hyper-intense (B,C). In the sagittal T2 sequences, involvement of the whole brain stem (nearly all of the midbrain, medulla, and the posterior part of pons) can be seen (D).

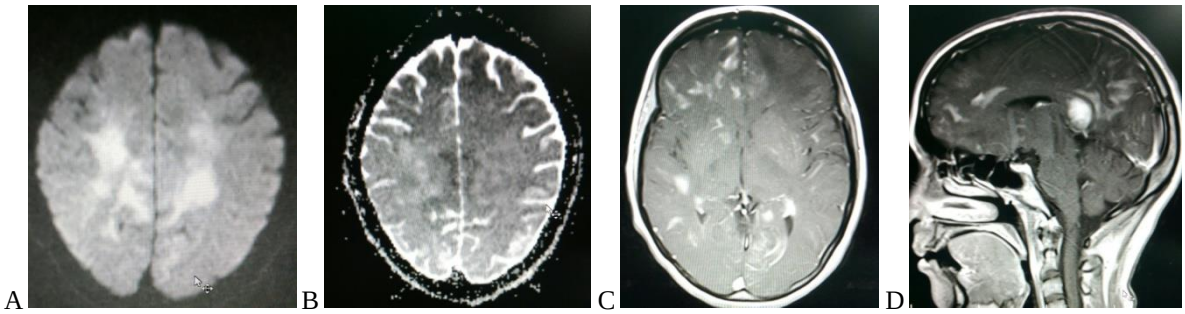


Figure 2. Diffusion-perfusion MRI show that bilateral restrictive pattern (A,B) in the axial and sagittal T1 sequences with contrast in most lesions have a homogeneous enhancement (C,D).

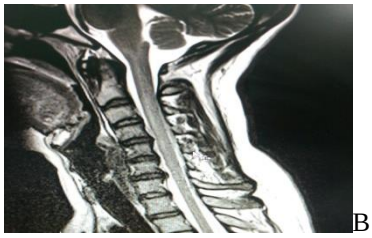
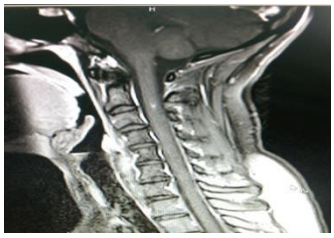
A  B 

Figure 3. The T2 sagittal sequences show a hyper-intense long lesion in the cervical spinal cord (A). The lesion has patchy enhancements in the T1 sequences (B).

After CSF collection, empirical treatment with antibiotics was started. Other diagnostic tests such as HIV antibody, wright, coombs wright, VDRL, 2ME from serum and PCR of TB, HSV, Brucella from CSF, smear, and culture of CSF, were negative. Based on these results, treatment with antibiotics was stopped. Based on the location of multiple lesions in the brain and the involvement of cervical spine, acute demyelinating encephalomyelitis (ADEM) was suggested. Therefore, IV methylprednisolone with a dose of 1 g per day for five days was started. After 48 hours of treatment, relative clinical improvement of signs was seen, and disorientation was improved; however, lateralized signs persisted. After 24 hours from the primary remission, the clinical signs got worse, and the level of consciousness decreased; therefore, the patient was intubated and the cyclophosphamide pulse was started. Another LP was performed, and CSF analysis showed the following results: WBC = 2(100% lymphocytes), glucose = 59, pro = 78. Also, PCR for CMV, JC virus, fungal panel, OCB, cytology, smear, and culture was performed, and all results were negative. The results of HIV P24 and RPR were also negative. MRI was repeated for the patient, and showed increased volume and edema of the lesions. To roll out malignancy and paraneoplastic syndrome, an abdomen, pelvic and para aortal sonography was performed, which did not show any abnormal findings. A marker assay with CA125, CA 19-9, CEA, and CA15-3 was performed, and the results were normal. After cyclophosphamide pulse, the patient was extubated and the level of consciousness improved partially, however, the patient had disorientation, dysphagia, and spastic quadriplegia. Because of the increased volume and constant enhancement of lesions (Figure 4), the patient was referred to another center for brain biopsy.

The results of the biopsy showed malignant large B-cell lymphoma (Figure 5).

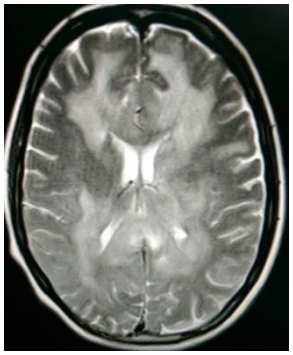
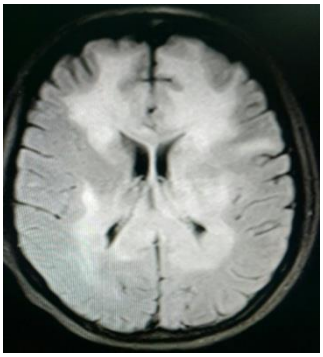
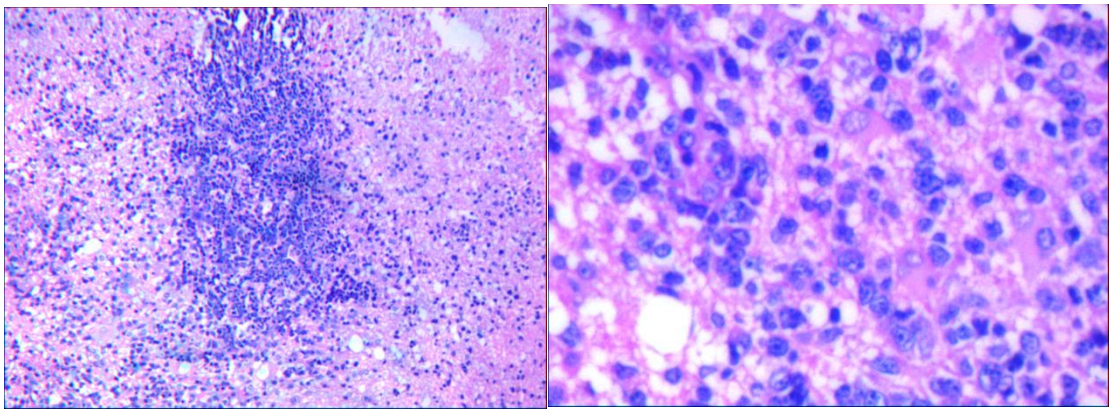
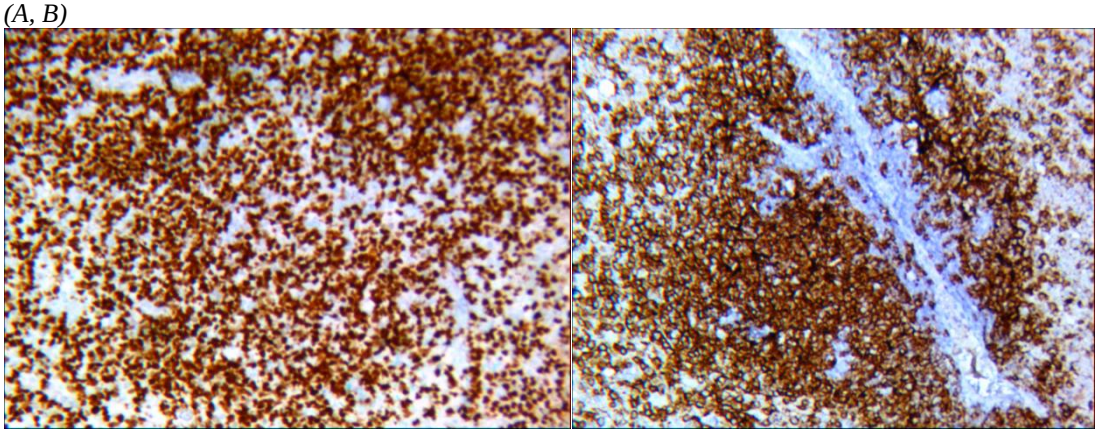
A  B 

Figure 4. Severe increase of the volume of the lesions can be seen in the axial T2 (A) and FLAIR sequences (B).



(A, B)



(C, D)

Figure 5. Microscopic examination revealed brain tissue infiltrated by high-grade lymphoid neoplasm. The tumor cells had large vesicular nuclei containing small to medium-sized nucleoli and irregular nuclear borders. They infiltrated cerebral tissue diffusely associated with the tight perivascular arrangement. Multiple mitoses and tingible body macrophage created starry sky appearance. Small lymphocytes were seen among tumor cells (A,B). IHC stains were positive for CD 45 and CD 20, and negative for CD 3, CD 30, and EMA. As a result, the brain tumor was diagnosed as a malignant large B-cell lymphoma (C,D).

After the biopsy, the patient's systemic status declined, and she went into shock with increased liver enzymes, urea, and creatinine, which made it impossible to receive chemotherapy with high-dose methotrexate and was expired 48 hours after receiving the biopsy result.

Discussion

PCNSL is a rare cerebral tumor (1). The strongest risk factor is immunodeficiency, which accounts for 20% of all lymphomas in patients with AIDS (11). In immunocompetent individuals, the risk of PCNS increases with aging (1) and the majority of the patients are within the age range of 50 to 70 years (5). Conversely, at ages above 65 years, the incidence rate of PCNS has increased, and this increase has been very significant in the oldest age group (75+ years). The incidence of this disease at different ages is also influenced by race. As reported, at the ages below 50 years, blacks have had higher overall incidence rates compared to whites. Also, the incidence rate of this disease was higher in men compared to women (0.55 per 100,000 persons per year vs. 0.39 per 100,000 person per year) (12).

Our patient was a 32-year-old woman with a negative history of immunodeficiency diseases, as well as a negative history of the use of immunosuppressive drugs. During her administration, HIV antibody was also checked and was negative. According to previous epidemiologic studies, the probability of incidence of PCNS in this age group, gender, and with normal immunity is very rare. Moreover, previous studies have reported that the diagnostic time after the initiation of clinical symptoms is between 3-6 months (7). In our case, this period was one month and a half, indicating the progressive nature of this disease in our patient. The initial symptoms of PCNSL such as personality change, depression, and disorientation, were found in our patient. However, later in the disease course, the signs of cranial palsy and brain stem involvement were noticed, which are seen in a few patients (6). The MRI showed multiple CNS involvement including periventricular regions, hemispheres, and corpus callosum, which are the most common involved areas (35-55% and 28-33%, respectively), and the brain stem which is less commonly involved area (18-25%). Also, in our patient, the cervical spine was involved which is a rare (1%) presentation of this tumor (13). In our case, lesion was multifocal. Multifocal involvement has been reported in 38.5% of patients with PCNS (14).

Studies have shown that the responsiveness of clinical symptoms to corticosteroid can highly be suggestive of this tumor (15), however, in our patient, this condition was not seen. On the other hand, the apoptotic effects of corticosteroids can mask the morphology of the tumor or even extinguish the tumor (7,8), and can prevent the histopathologic diagnosis of the tumor up to 50% (16). Therefore, suspected cases of PCNSL should not receive corticosteroid before biopsy (5). However, a retrospective study performed on 109 patients diagnosed with PCNSL from 1985 to 2005 showed that most of the patients had used corticosteroids before the diagnostic biopsy, indicating that the consumption of corticosteroids did not influence radiologic findings and there was no indication for repeated biopsy (13). Fortunately, in our case, a high dose of corticosteroids did not disturb the diagnosis of biopsy. The basis of treatment is high-dose methotrexate (HD-MTX)-based chemotherapy and whole-brain radiation. The nature of the disease is aggressive, and the 5-year survival rate has been reported 26%, although it has been reported to have had a higher incidence rate in recent years (31%) and in younger individuals (<49 years) (12). Poor survival rate includes age >60 years, Eastern Cooperative Oncology Group (ECOG) performance status >1, high LDH, high CSF protein, and deep brain involvement (17). Unfortunately, despite the diagnosis of the disease, our patient was expired.

Results

Although primary central nervous system lymphoma (PCNSL) is an uncommon CNS tumor and rarely occurs in individuals with immunocompetent, it should be considered as a differential diagnosis of neurologic diseases.

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