Case Report

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A case of primary central nervous system lymphoma mimic neuromyelitis optica

Abstract: Primary central nervous system lymphoma (PCNSL) is rare. And the symptoms of PCNSL are atypical, it is extremely easy to be misdiagnosed as other diseases. However, early treatment is crucial which is requesting early diagnosis. We report a case of a 47-year-old man who was initially diagnosed as neuromyelitis optica (NMO) on the basis of clinical findings, slightly high Aquaporin4 (AQP4) (1:10) and high signals of magnetic resonance imaging. Though his symptoms progressively improved after steroid pulse treatment, but worse when steroid was decreased to 40 mg per day. We considered the patient should be diagnosed as PCNSL. After the examination of magnetic resonance spectroscopy (MRS) and positron emission tomography (PET), the results indicated PCNSL was most possible. Therefore we gave him stereotactic biopsy of deep of supratentorial, which showed non-Hodgkin malignant B-cell lymphoma.

Keywords: Lymphoma, Neuromyelitis optica, primary central nervous system, case report, PCNSL

1 Introduction

Primary central nervous system lymphoma (PCNSL) is rare [1]. The symptoms of PCNSL are atypical as was easy to be misdiagnosed as other diseases [2]. There are some cases of PCNSL that are misdiagnosed as other diseases, such as Parkinson’s disease, myasthenia and multiple sclerosis [3]. There are some reasons. First, PCNSL represents less than 2% of all brain neoplasms and 1%–2% of malignant lymphomas. Most are B cell non-Hodgkin lymphoma (NHL), which may present as single or multiple lesions involving the eye, leptomeninges, or brain parenchyma. Localization primarily in the brain stem occurs in 3% of PCNSL, and most are T cell in origin [4]. In the present work, we present a rare case of primary central nervous system lymphoma which mimic neuromyelitis optica.

2 Case Report

A 47-year-old man presented with a 1-week history of neck pain and 2-day history of shoulders pain. He showed upper limb weakness and under the right chest numbness. However, He had no history of smoking and drinking, as well as persistent weight loss. He also denied the history of hypertension and diabetes.

On neurological examination, the patient was found to have a shallow of the left frontal line and nasolabial groove and hypaesthesia under T4 the right chest. Muscular tension was normal, but upper limbs muscle strength was 4-/5 and lower limbs muscle strength was 5-/5. Tendon reflexes were normal and both Kernig’s and Brudzinski’s signs were negative, but bilateral Babinski signs and left Hoffmann sign were positive. Analyses of viral antibodies, syphilis serology, and human immunodeficiency virus antibodies were negative. Lumbar puncture showed normal intracranial pressure. In the CSF findings (Table 1), tumor cells were not observed. Red cells were 10/ul and nuclear cells were 220/ul, however, the classification flow cytometry of cerebrospinal fluid leukemia had not found abnormal differentiation of cells. The protein level was slightly elevated (91 mg/dL), however, chloride (127 mmol/L) and glucose (3.32 mmol/L) were normal. Oligo-clonal bands were not present. Other markers of autoimmune diseases, such as antinuclear antibodies, extractable nuclear antigen, and antineutrophil cytoplasmic antibodies, were all negative. However, some cytokines were slightly high (IL-2(0.1pg/ml), IL-6 (67.75 pg/ml), TNF-α (50.66pg/ml), others (IL-2, IL-10, IL-17 and IFN-γ) were normal. Serum anti-AQP4 antibodies were slightly positive (1:10) on April 6th 2016,
A case of primary central nervous system lymphoma mimic neuromyelitis optica (NMO) which was consistent with the diagnosis of NMO. Magnetic resonance imaging of the cervical spinal cord revealed multiple lesions occupied in C2-T1 spinal and brain stem, high in T2 weighed, enlargement of the cervical spinal and evident enhancement in the enhanced imaging (Figure 1). Magnetic resonance scans showed bilateral thalamus, periventricular, basal ganglia, pedunculus cerebri with hypersignals using fluid-attenuated inversion recovery (Figure 2 A and B). Combination of the clinical symptoms, neurological examination, laboratory examination and magnetic resonance imaging, the initial diagnosis was considered as neuromyelitis optica with steroid pulse treatment (methylprednisolone 1g intravenous injection per day) and immunoglobulin. After steroid treatment, his symptoms progressively improved and he returned home.

However, when steroid was decreased to 40 mg per day, his symptoms worsened and he was admitted to our hospital again. He presented with limbs weakness, spirit weakness and vision loss in the left eye in 2 months. His limb muscle strength gradually declined to grade 0 2 months later. Review serum anti-AQP4 antibodies were negative on May 20th 2016. Magnetic resonance imaging revealed that right basal ganglia, pons, cerebellar peduncles with hypersignals, and lesions were larger than 2 months ago (Figure 2 C, D, E and F). The MRS showed a high resonance of free lipids and Cho/NAA ratio (4.8-5.1), lactates were also visible, which was in favor of a tumoral process (Fig 4). Positron emission tomography (PET) showed a slightly increased 18-Fludeoxyglucose (18F-FDG) uptake in the right basal ganglia and right pons and obviously increased uptake of 18F-FDG in the affected brain, the maximum SUV (Standardized Uptake Value) value is 23.6, indicating PCNSL possible (Figure 1E and Figure 2C). (May 27th) Stereotactic biopsy of deep of supratentorial was performed and immunohistochemical analysis showed that the brain tissue was infiltrated with multiple foci of heterotypic cells with CD20 (+), 6-1 CD79a (+), Ki-67 (90%+++), BcL-2 (80%+) (Figure 5), suggestive of non-Hodgkin malignant B-cell lymphoma. (May 29th) After a stereotactic biopsy, the patient appeared unconscious. Arterial blood gas showed partial pressure of carbin dioxide (pCO2) elevated. After endotracheal intubation and mechanical ventilation, the patient’s pCO2 gradually

Table 1. The results of the CSF findings

| Examination                        | CSF/serum | Results |
|-----------------------------------|-----------|---------|
| Tumor cells                       | CSF       | Negative|
| Red cells                         | CSF       | 10/ul   |
| Nuclear cells                     | CSF       | 220/ul  |
| Protein                           | CSF       | 91mg/dL |
| Glucose                           | CSF       | 3.32mmol/L|
| Oligo-clonal bands                | CSF       | Negative|
| Antinuclear antibodies            | serum     | Negative|
| Extractable nuclear antigen       | serum     | Negative|
| Antineutrophil cytoplasmic antibodies | serum   | Negative|
| Il-2                              | serum     | 0.1pg/ml|
| Il-6                              | serum     | 67.75pg/ml|
| TNF-α                             | serum     | 50.66pg/ml|
| Anti-aqp4 antibodies              | serum     | Positive|

CSF: cerebrospinal fluid
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m2) and the hypaesthesia plane was down to T2 the right chest. Then he has given rituximab 600 mg and the second course of Methotrexate at a high dose (5 g/m2). After the third course of methotrexate cycle, his symptoms were not improved further. He was given intrathecal injection of MTX 15mg + Ara-e 50mg + DXM10 mg. Later, CT scan image, compared to 2016-05-29 CT image, bleeding fade, edema reduced, which also supported the previous diagnosis of 

Figure 2. Magnetic resonance imaging revealed that right basal ganglia, pons, cerebellar peduncles with abnormal signals. (April 5th) A and B: Magnetic resonance scans showed bilateral thalamus, periventricular, basal ganglia, pedunculus cerebri with hypersignals using fluid attenuated inversion recovery. (May 19th) C: Positron emission tomography (PET) showed a slightly high enhancement in the right basal ganglia and right pons, about the size of which is 2.1*2.0*2cm and the maximum SUV value is 23.6. (May 23th) D, E, F and G: A month and a half later, axial T1 and T2 magnetic resonance imaging revealed that right basal ganglia, pons, cerebellar peduncles with hypersignals, and lesions were larger than the former, even involved in bilateral thalamus. This enlargement would be suggestive of a neoplastic process. (July 20th) H: Axial T2 magnetic resonance imaging revealed that right basal ganglia, pons, cerebellar peduncles with abnormal signal, compared with 2016-05-23, lesions decreased.

Figure 3. CT scan showed the right basal ganglia and right temporal lobe hemorrhage with edema (May 29th) A: Brain CT scan showed the right basal ganglia flake slightly higher density, CT value of about 32U, surrounding low-density, right temporal lobe low-density, the intracranial brain parenchyma density was not significantly abnormal changes. Midline slightly shifted to the left. (June 14th) B and (June 27th) C: Brain CT scan image is about similar to the image in 5.29, bleeding fade, edema reduced.
3 Discussion

Primary central nervous system lymphoma (PCNSL) is rare clinically without the exact incidence rate [1]. PCNSL is not firstly considered in most of the clinical cases because we often diagnose diseases as single and common diseases. In the usual case of neurologists, PCNSL are usually the last to consider. Second, PCNSL may present with all symptoms, such as limb weakness, hemianopsia, hypersomnia, and binocular vertical diplopia. Though typical optic neuromyelitis showing acute severe long myelitis and bilateral or simultaneous symptoms, some patient’s symptoms may slowly progress from one side to the other. Symptoms can prompt us for some disease, but not the only criteria for diagnosing the disease. So we diagnose diseases with a combination of symptoms, laboratory tests and radiographic. Third, some laboratory tests may be also prone to other diseases. Although the

![Figure 4](image_url)

*Figure 4. The MRS showed a high resonance of free lipids and Cho, a low resonance of NAA, and a high Cho/NAA ratio (4.8-5.1).*

![Figure 5](image_url)

*Figure 5. Pathology of the brain showing: (Right basal brain tissue): Non-Hodgkin’s lymphoma, Diffuse large B cell type. CD3 (-), CD20 (+), 6-1 CD79a(+), CD30(Ki-1)( -), CD5(-), CD10(-), Bcl-2 (80%+), Bcl-6 (-), ALK(-), MUM1 (+), Ki-67 (90%+++), PAX-5 (+), Myc (40%+), CyclinD1 (-).*
NMO is also not frequently diagnosed clinically with the incidence of 2.56 out of 100,000 persons [5]. NMO-IgG has been reported to be a novel serological marker for NMO [6]. But there have been several case reports of NMO-IgG coincident with cancer, suggesting NMO-IgG possibly being a paraneoplastic marker [7-9]. Neoplastic cells may provide the antigen initiating an aquaporin-4 immune response. Tumor cells express, as onconeural antigens, proteins that are normally expressed by mature neurons, glia, or muscle. Cancer-directed immune responses initiated by those antigens have the potential to target autoantigens in the nervous system [10]. In this case, AQP4 serum-positive(1:10) may be caused by PCNSL rather than NMO. But it is not denied that AQP4 serum-positive can help diagnose NMO. Finally, the radiographic examination maybe not typical in some cases. The radiographic of the patient was over three vertebral segments, slightly high in T2 weighted and enlargement of the cervical spinal, which is not typical. The radiological spectrum of the CNS lesion in NMO is very wide. Longitudinally extensive transverse myelitis, over 3 vertebral segments, and optic neuritis, extensive and involving posterior segment, are essential findings for the diagnosis [11]. So the current case is an unusual presentation of primary brain stem B cell non-Hodgkin’s lymphoma, which was initially misdiagnosed as NMO on the basis of clinical findings, slightly high AQP4 and magnetic resonance imaging that accorded with the characteristic imaging of NMO. This case needs to attach clinical neurologists great attention to some points: when we diagnose a patient as NMO, we also should differentiate from PCNSL. We need other more effective methods to help differentiate NMO and PCNSL. By assessing some metabolic changes for many pathological processes, localized Proton Magnetic Spectroscopy (MRS) has been successfully used as a more sensitive and non-invasive tool for differential diagnosis [12]. In some cases, after the steroid pulse treatment, the symptoms are still progressive, we could suggest patient to have a test of MRS. If the MRS of the patient shows a high resonance of free lipids and visible lactate, especially a high Cho/NAA ratio, PCNSL should be considered [12]. Except for MRS, it showed that the CSF sIL-2R level is a biomarker that can differentiate CNS IDDs (inflammatory demyelinating diseases) from CNS lymphoma. CSF sIL-2R is founded higher than in the patient of PCNSL than of CNS IDDs [13]. NMO is one of CNS IDDs, so CSF sIL-2R maybe also can help differentiate PCNSL from NMO. However, the final diagnose is needed a stereotactic biopsy. Immunohistochemical analysis not only can help diagnose the patient as PCNSL, but also can certain the pathological type. All these tests can help differentiate CNS lymphoma from NMO, but most important thing is that we have a concept that we should differentiate a common diagnose from PCNSL and we know the best time when we should give the patient the examination of MRS, CSF sIL-2R and stereotactic biopsy.

There are several possible causes of this patient’s intracranial hemorrhage. First, the most likely cause of intracranial hemorrhage in this patient is puncture bleeding according to the history of stereotactic biopsy and the CT image after two weeks. And it is also based on the site of intracranial hemorrhage in the puncture site. Second, the patient’s intracranial hemorrhage cannot rule out the possibility of tumor necrosis bleeding because of the PCNSL invasion of the basal ganglion. Intratumoral hemorrhage may be seen, which is rare in the immunocompetent patient [14]. This patient’s analyses of viral antibodies, syphilis serology, and human immunodeficiency virus antibodies were negative. The possibility of intratumoral hemorrhage is small. Third, it may also be due to thrombocytopenia caused by chemotherapy drugs, such as Methotrexate, which induce intracranial hemorrhage. However, this patient tested blood routinely, so this possibility is also small.

Conflict of interest: Authors state no conflict of interest

References

[1] Ostrom QT, Cioffi G, Gittleman H, Patil N, Waite K, Kruchko C, et al. CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2012-2016. Neuro Oncol 2019;21:v1-v100.
[2] Fox CP, Phillips EH, Smith J, Linton K, Gallop-Evans E, Hemmaway C, et al. Guidelines for the diagnosis and management of primary central nervous system diffuse large B-cell lymphoma. Br J Haematol 2019;184:348-363.
[3] Citterio G, Calimeri T, Ferreri A. Challenges and prospects in the diagnosis and treatment of primary central nervous system lymphoma. Expert Rev Neurother 2018:1-15.
[4] Shams PN, Waldman A, Plant GT. B Cell lymphoma of the brain stem masquerading as myasthenia. J Neurol Neurosurg Psychiatry 2002;72:271-3.
[5] Kim JE, Park SH, Han K, Kim HJ, Shin DW, Kim SM. Prevalence and incidence of neuromyelitis optica spectrum disorder and multiple sclerosis in Korea. Mult Scler 2019:135248519888609.
[6] Lennon VA, Wingerchuk DM, Kryzer TJ, Pittock SJ, Luchinetti CF, Fujihara K, et al. A serum autoantibody marker of neuromyelitis optica: distinction from multiple sclerosis. Lancet 2004;364:2106-12.
[7] De Santis G, Caniatti L, De Vito A, De Gennaro R, Graniere E, Tola MR. A possible paraneoplastic neuromyelitis optica associated with lung cancer. Neurol Sci 2009;30:397-400.
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[8] Mueller S, Dubal DB, Josephson SA. A case of paraneoplastic myelopathy associated with the neuromyelitis optica antibody. Nat Clin Pract Neurol 2008;4:284-8.

[9] Antoine JC, Camdessanche JP, Absi L, Lassablière F, Féasson L. Devic disease and thymoma with anti-central nervous system and antithymus antibodies. Neurology 2004;62:978-80.

[10] Pittock SJ, Lennon VA. Aquaporin-4 autoantibodies in a paraneoplastic context. Arch Neurol 2008;65:629-32.

[11] Wingerchuk DM, Banwell B, Bennett JL, Cabre P, Carroll W, Chitnis T, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology 2015;85:177-89.

[12] Taillibert S, Guillemin R, Menuel C, Sanson M, Hoang-Xuan K, Chiras J, et al. Brain lymphoma: usefulness of the magnetic resonance spectroscopy. J Neurooncol 2008;86:225-9.

[13] Ikeguchi R, Shimizu Y, Shimizu S, Kitagawa K. CSF and clinical data are useful in differentiating CNS inflammatory demyelinating disease from CNS lymphoma. Mult Scler 2018;24:1212-1223.

[14] Tang YZ, Booth TC, Bhogal P, Malhotra A, Wilhelm T. Imaging of primary central nervous system lymphoma. Clin Radiol 2011;66:768-77.