TITLE:
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CASE REPORT

Recurrent Epstein-Barr Virus-positive (EBV+) Primary Central Nervous System Lymphoma (PCNSL) in a Patient with Clinical Features of Chronic Lymphocytic Inflammation with Pontine Perivascular Enhancement Responsive to Steroids (CLIPPERS)

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Abstract:
Primary central nervous system lymphoma (PCNSL) and chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) can share clinical features and may be indistinguishable, even after brain biopsy. We encountered a case of Epstein-Barr virus-positive (EBV+) PCNSL recurrence in a patient with clinical features of CLIPPERS, and repeat brain biopsy was required to reach the correct diagnosis. Four years after the initial diagnosis and treatment of PCNSL, “peppering” punctate enhanced lesions with transient steroid responsiveness were detected during brain magnetic resonance imaging (MRI). A second brain biopsy supported a diagnosis of CLIPPERS, while a third biopsy confirmed the diagnosis of recurrent PCNSL.

Key words: primary central nervous system lymphoma (PCNSL), chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS), recurrence, repeat brain biopsy, Epstein-Barr virus (EBV)

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Introduction

Primary central nervous system lymphoma (PCNSL) is a brain tumor with various clinical features that accounts for approximately 3% of all brain tumors (1). Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) is a relatively new brain inflammatory disease that was first described by Pittock et al. in 2010 (2). This condition has the characteristics of steroid responsiveness, a punctate peppering enhancement pattern that is predominantly observed in the brain stem during magnetic resonance imaging (MRI), and perivascular T-cell infiltration in the pathological specimens (2). Interestingly, CLIPPERS and PCNSL can have similar clinical and radiological features, and brain biopsy plays an important albeit not always definitive role in distinguishing PCNSL from CLIPPERS (3-5). Brain biopsy may be unnecessary for patients with typical clinical and radiological findings of CLIPPERS, although brain biopsy is strongly recommended in cases with warning signs that include steroid resistance, asymmetrical brain stem lesions, and marked B symptoms (6). Three case reports have described patients with PCNSL who were initially diagnosed with CLIPPERS be-

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cause they exhibited a remarkable initial response to steroid treatment and the findings from the first brain biopsy were compatible with CLIPPERS (3-5). We report a case of recurrent Epstein-Barr virus-positive (EBV+) PCNSL with clinical features that mimicked CLIPPERS, in which the correct diagnosis of PCNSL required close clinical observation and repeat brain biopsy.

Case Report

A 41-year-old-man with no medical history presented with a 2-week history of subacute dysarthria and bilateral lower-limb muscle weakness. A clinical examination revealed dysarthria, lower-limb paresis, and left-side upper limb ataxia. Extensive laboratory investigations, including a test of the patient’s soluble interleukin-2 receptor level (sIL-2R; 211 U/mL), revealed normal findings. The patient’s serum was positive for Epstein-Barr virus (EBV) viral capsid antigen (VCA) IgG (a titer of 80) and Epstein-Barr nuclear antigen IgG (titer: 10), but negative for EBV VCA IgM (titer: <10) and Epstein-Barr virus-early antigen, diffuse type and restricted type (EA-DR) IgG (titer: <10), which suggested a possible history of EBV infection. A cerebrospinal fluid (CSF) analysis revealed a mildly elevated cell count (72/μL) and protein level (80 mg/dL), but negative cytology results. Brain and spine MRI revealed punctate hyperintense lesions predominantly in the cerebellar region that involved the brachium pontis, pons, and spinal cord, with enhancement after the administration of gadolinium (Fig. 1A and B). In addition, [18F]-fluorodeoxyglucose positron emission tomography (FDG-PET)-computed tomography (CT) fusion imaging revealed an increased uptake in the cervical region and thoracic spinal cord. These findings supported the suspicion of neuroinflammatory disease, and the patient was treated with two 3-day cycles of intravenous methylprednisolone (1,000 mg). However, there was no clear clinical or radiological improvement (Fig. 1C and D), although bilateral lower-limb paresis and restricted type (EA-DR) IgG (titer: <10), which suggested a possible history of EBV infection. A cerebrospinal fluid (CSF) analysis revealed a mildly elevated cell count (72/μL) and protein level (80 mg/dL), but negative cytology results. Brain and spine MRI revealed punctate hyperintense lesions predominantly in the cerebellar region that involved the brachium pontis, pons, and spinal cord, with enhancement after the administration of gadolinium (Fig. 1A and B). In addition, [18F]-fluorodeoxyglucose positron emission tomography (FDG-PET)-computed tomography (CT) fusion imaging revealed an increased uptake in the cervical region and thoracic spinal cord. These findings supported the suspicion of neuroinflammatory disease, and the patient was treated with two 3-day cycles of intravenous methylprednisolone (1,000 mg). However, there was no clear clinical or radiological improvement (Fig. 1C and D), which supported the suspicion of another etiology, such as PCNSL.

Biopsy of the enhanced cerebellar lesion was performed, and the specimen exhibited perivascular lymphocytic infiltration (Fig. 2A) with a small number of large atypical cells in a high-power field (Fig. 2B). Immunohistochemistry revealed that the perivascular lymphocytes consisted of CD20+ B-cells (Fig. 2C) and CD3+ T-cells (Fig. 2D), without monotonous lymphocytic proliferation, and the Ki-67 labeling index was approximately 5% (Fig. 2E). Flow cytometry and karyotyping were not performed. Although the historical findings were inconclusive, based on the small number of atypical cells, the patient’s clinical course appeared more compatible with PCNSL than neuroinflammatory disease, and the inconclusive pathological result was potentially attributed to the previous steroid treatment. Thus, PCNSL treatment was started using six cycles of high-dose methotrexate and cytarabine-based chemotherapy, plus total spinal cord radiotherapy for the residual spinal lesions, which was followed by high-dose chemotherapy supported by autologous stem cell transplantation. These treatments provided moderate clinical improvement and complete radiological remission based on the brain MRI findings (Fig. 1E and F) (7), although bilateral lower-limb paresis persisted as a sequela due to the spinal cord lesions.

Four years after the initial PCNSL treatment, brain MRI revealed recurrent “peppering” punctate enhancing lesions in...
the cerebellum (Fig. 1G and H) and an additional enhancing lesion in the right frontal white matter (Fig. 3A and B) with no uptake of FDG. A neurological examination revealed slight left-upper extremity ataxia and persistent bilateral lower-limb paresis. Extensive laboratory investigations revealed that the autoimmune antibody and tumor marker levels were within the normal limits, with the exception of a slightly elevated sIL-2R level (644 U/mL) and an elevated IgE level (1,540 IU/mL). The level of serum EA-DR IgG was elevated (titer: 160); no other EBV serology parameters were tested. Testing of the CSF revealed a non-elevated cell count (<11/μL), a mildly elevated protein level (58 mg/dL), and a normal IgG index (0.53), with no oligoclonal band and negative cytology results. Because the clinical symptoms were insignificant and brain MRI revealed the slow progression of the lesions, we considered the results to be atypical for recurrent PCNSL and elected to perform careful observation without treatment.

At 6 months after the appearance of radiological abnormalities, we performed a second brain biopsy, which revealed perivascular lymphocytic infiltration with a lower cell density than the first biopsy specimen (Fig. 3C). There were no apparent atypical cells in a high-power field of the second specimen (Fig. 3D). Immunohistochemistry revealed that most of the infiltrating lymphocytes were CD3+ T-cells (Fig. 3F) and that no CD20+ B-cells were present (Fig. 3E). The specimen was considered to have non-specific inflammatory changes with no evidence of malignancy, demyelination, granuloma, or vasculitis (Fig. 3C-E), and the histological evaluation revealed only reactive changes due to inflammation. Flow cytometry of the biopsied specimen revealed no population of monoclonal cells. Although the possibility of recurrent PCNSL could not be completely excluded, the slowly progressing clinical course and absence of malignant cells in the biopsy specimen - even after 6 months of clinical observation without any treatment - made the diagnosis of recurrent PCNSL less likely. The alternative diagnosis - based on the distribution of the radiological enhancement and a clinical course that would be considered atypical for recurrent PCNSL - was CLIPPERS. The patient was treated using two 3-day cycles of intravenous methylprednisolone (1,000 mg) every other week, which was followed by oral prednisolone (60 mg/day). There was a marked decrease in the size of the brain lesions after the steroid treatment (Fig. 1I and J), and a slight improvement of the bilateral lower-limb paresis, which were both considered compatible with the response of CLIPPERS to treatment. The dosage of prednisolone was slowly reduced by 10 mg every 2 weeks to a dose of 30 mg, and then by 5 mg every 4 weeks to a dose of 20 mg.

However, at 6 months after the start of steroid treatment, brain MRI revealed an exacerbation of the brain lesions...
Figure 3. The second biopsy of the frontal lobe revealed non-specific inflammation that clinically suggested CLIPPERS. (A) Gadolinium-enhanced T1-weighted brain magnetic resonance imaging before the biopsy revealed the right frontal enhanced lesion. (B) Gadolinium-enhanced T1-weighted MRI of the brain after the biopsy. (C) Perivascular lymphocytic infiltration (Hematoxylin and Eosin staining), (D) but no atypical cells in a high-power field from (C). Staining for (E) CD20 and (F) CD3. Bars indicate 100 μm (C) or 50 μm (D-F). CLIPPERS: chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids.

(Fig. 1K and L), and we re-started 3-day intravenous methylprednisolone treatment (1,000 mg). However, the lesions gradually worsened, which prompted us to perform a third biopsy of the cerebellum. The specimen exhibited numerous lymphocytes aggregating to the Virchow-Robin spaces (Fig. 4A), with “perivascular cuffing”, which is a characteristic feature of diffuse large B-cell lymphoma (DLBCL) in the central nervous system (CNS). A high-power field revealed diffuse proliferation of large lymphoid cells with irregular nuclei, fine chromatin, and prominent nucleoli (Fig. 4B). Immunohistochemistry revealed that the infiltrating cells were CD20+ B-cells (Fig. 4C) with almost no CD3+ T-cells (Fig. 4D) and that the Ki-67 labeling index was 70% (Fig. 4E). EBV involvement was confirmed using in situ hybridization of EBV-encoded RNA (EBER) (Fig. 4F). A polymerase chain reaction (PCR) detected no EBV DNA in the serum or CSF. Flow cytometry revealed a clonal B-cell population with a phenotype of CD19+, CD20+, Sm-IgG+, and HLA-DR+. Southern blotting confirmed monoclonal IgH gene rearrangement, which led to the definitive diagnosis of PCNSL. A chromosomal analysis revealed no abnormalities. We attempted to retrospectively detect EBV in the first and second biopsy specimens using a PCR and in situ hybridization; however, these attempts did not identify EBV, which could be attributed to the scarcity of tumor cells and the deterioration of the sample.

Discussion

We encountered a patient with recurrent PCNSL who exhibited clinical features that resembled CLIPPERS. The clinical course of this case highlights two important issues. The first issue is that atypical recurrence of PCNSL can involve clinical features that resemble CLIPPERS. The second issue is that repeat brain biopsy is useful for distinguishing PCNSL from CLIPPERS.

We are aware of three reported PCNSL cases that involved an initial diagnosis of CLIPPERS (3-5); however, our case appears to be the first to involve recurrent PCNSL with the clinical features of CLIPPERS. These features are steroid responsiveness, a punctate peppering enhancement pattern that is predominantly observed in the brain stem during MRI, and perivascular T-cell infiltration (2). In the present case, the first cerebellar biopsy revealed a mixture of B-cells and T-cells. Although the histological findings did not conclusively support a diagnosis of PCNSL, we attributed this negative biopsy result to the previous steroid therapy. In a previous report, steroid treatment obscured a histological diagnosis of PCNSL in >30% of patients who received ≤1 week of steroid treatment and in >50% of patients who re-
Figure 4. The third biopsy of the cerebellum confirmed PCNSL. (A) Perivascular lymphocytic infiltration (Hematoxylin and Eosin staining) and (B) large lymphoid cells with irregular nuclei, fine chromatin, and prominent nucleoli in a high-power field from (A). Staining for (C) CD20, (D) CD3, and (E) Ki-67 (labeling index: 70%). (F) In situ hybridization of Epstein-Barr virus-encoded RNA (EBER-ISH). Bars indicate 100 μm (A, E) or 25 μm (B-D, F). PCNSL: primary central nervous system lymphoma.

cieved longer steroid treatment, versus a failed diagnosis rate of <10% among patients who did not receive steroid treatment (8). We hypothesize that the steroid treatment also affected our findings regarding the first biopsy specimen and resulted in a clinical diagnosis of PCNSL based on the poor response to the steroid therapy being incompatible with the presence of a neuroinflammatory disorder. Our patient also experienced radiological relapse at 4 years after treatment, which involved MRI findings that were similar to the initial findings. However, given the slow progression of the disease, which seemed atypical for recurrent PCNSL, we considered the possibility of another etiology and performed a second brain biopsy of the right frontal lobe lesion, which revealed no evidence of malignancy. Interestingly, the core features of CLIPPERS are similar to the radiological punctate peppering enhancement pattern in the brachium pontis and cerebellum, as well as the remarkable steroid response and non-specific inflammatory findings (2, 9). Thus, the previously reported cases involved misdiagnoses of CLIPPERS based on transient steroid responsiveness and the presence of T-cell infiltration without malignant B-cells (3-5). Thus, the possibility of steroid resistance should be carefully monitored, even if CLIPPERS is diagnosed based on the absence of malignant B-cells in the biopsy specimen, and relapse during steroid therapy may indicate that re-biopsy is needed to rule out the possibility of PCNSL.

The EBER-positive result from the third biopsy is another characteristic feature of our case. Two previous reports have described EBER-positive CNS-lymphomatoid granulomatosis (CNS-LYG) that was initially diagnosed as CLIPPERS (15, 16). However, the third biopsy specimen from our patient did not have angiodestructive lesions that might be suggestive of CNS-LYG, and the histology was typical for DLBCL of the CNS. Thus, the final diagnosis of our case was EBV+ DLBCL, NOS based on the revised 4th edition of the World Health Organization classification (17).

Our patient had a positive serological result for EA-DR IgG at 4 years after the initial diagnosis and treatment of PCNSL appear more reasonable.

Although the key difference between PCNSL and CLIPPERS involves their pathological features, it can be difficult to correctly diagnose PCNSL based on brain biopsy findings, which are confounded by “sentinel lesions” or previous steroid treatment (12-14). Similarly, the previously reported cases involved misdiagnoses of CLIPPERS based on transient steroid responsiveness and the presence of T-cell infiltration without malignant B-cells (3-5). Thus, the possibility of steroid resistance should be carefully monitored, even if CLIPPERS is diagnosed based on the absence of malignant B-cells in the biopsy specimen, and relapse during steroid therapy may indicate that re-biopsy is needed to rule out the possibility of PCNSL.
PCNSL. This parameter usually becomes elevated during EBV reactivation (18). Interestingly, one report described a case of CLIPPERS in which EBV infection led to a dramatic elevation of the EBV DNA level in the CSF, while a PCR failed to detect EBV in the serum and no EBV involvement was detected in a brain biopsy specimen using in situ hybridization of EBER (19). Moreover, several reported cases of CLIPPERS have occurred in patients with immunosuppressive backgrounds, such as patients with history of chemotherapy or steroid use, which may be involved in EBV reactivation (16, 19, 20). Given the features of our case and the reported cases, EBV infection or reactivation in the CNS may be associated with the core features of CLIPPERS (i.e., punctate “peppering” enhanced lesions or perivascular T-cell infiltration), which are also observed in cases of EBV+ DLBCL or CNS-LYG.

In conclusion, we encountered a case involving a patient with recurrent PCNSL who exhibited the clinical features of CLIPPERS, and in which repeat brain biopsy was needed to correctly diagnose PCNSL. Thus, even if a patient exhibits atypical clinical and radiological features of PCNSL, which might suggest the presence of core features of CLIPPERS, we recommend primarily considering recurrent PCNSL if the patient has a history of PCNSL. It is also possible that PCNSL exists in patients with a tentative diagnosis of CLIPPERS, because of the possibility of a transient response of PCNSL to steroid treatment.

The authors state that they have no Conflict of Interest (COI).

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